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United Services Section

President—Sir GORDON GORDON-TAYLOR, K.B.E., C.B., F.R.C.S.

[*June* 5, 1952]

Modern Views on the Prevention of Tetanus in the Wounded

By Brigadier A. SACHS, C.B.E., M.D., M.Sc., Q.H.P.

THE Army Pathology Advisory Committee has recently recommended that wounded soldiers who have been actively immunized should be given a dose of tetanus toxoid and not tetanus antiserum as has been the practice previously. The recommendation has been accepted and this paper will discuss the development of prophylactic immunization against tetanus from 1914 to the present day, including the findings of investigations carried out during 1951 which have led to the change in British Army Policy.

THE WAR OF 1914–18: PASSIVE SERUM PROPHYLAXIS AGAINST TETANUS (HISTORY OF THE GREAT WAR, 1923)

On the outbreak of war only small quantities of prophylactic tetanus antiserum were available, since the experience of the South African and Russo-Japanese wars had suggested that tetanus was unlikely to be an element of great importance. As a result, the incidence of tetanus in the wounded was over 8 per 1,000 during the early months of the war—an incidence similar to that recorded for the Northern theatre in the Franco-German War of 1870–71. Great efforts were made by the War Office to provide serum on a scale sufficient to ensure a prophylatic inoculation for every wounded man. By the end of November ample supplies were available and the incidence of tetanus fell to about 1 per 1,000, when all at risk were given prophylactic treatment. The average incidence of the disease on the Western Front during the four years of war was 1·47 per 1,000.

Nearly all the antiserum used was obtained from British and American sources, standardized in terms of the United States unit (the equivalent of the International Unit 1950) and issued in glass phials which contained 10 ml. of antiserum (= 1,500 units). Each patient usually received 500 units which was the dose recommended by the War Office Tetanus Committee to be given as soon as possible after wounding.

In order to reduce the incidence of tetanus still further, the Director-General, Army Medical Services in France, in 1916, recommended the larger dose of 1,000 units for lacerated wounds. In June 1917 instructions were issued that four prophylactic inoculations should be given at intervals of seven days. In June 1918, Sir William Leishman, Adviser in Pathology in France, recommended that the initial prophylactic dose should be increased to 1,500 units in order to prolong the period of high concentration in the blood. Sir David Bruce, however, maintained that 500 units was adequate if subsequent doses could be guaranteed. On the cessation of hostilities the data available was insufficient to permit the drawing of any conclusions. The recommendations made by Leishman and Bruce form the basis of modern passive prophylaxis against tetanus.

The value of passive prophylaxis in tetanus may be assessed from the following observations:

(*a*) The rapid reduction in incidence from 8 per 1,000 during the first months of the war to 1 per 1,000 after the giving of antiserum to all at risk (*see above*).

(*b*) The reduction in mortality, consequent upon the increased incubation period. An interesting result of the use of prophylactic antiserum was the change in type of tetanus seen to "local tetanus" which rarely occurred prior to 1914 and during the early months of the war. During the rest of the war "local tetanus" occurred as a relatively common phenomenon.

The high value of passive prophylaxis would appear to be the outstanding fact of the history of tetanus in the European War of 1914–18.

THE INTER-WAR YEARS: DEVELOPMENT OF ACTIVE IMMUNIZATION AGAINST TETANUS

The principle of active immunization is the establishment of basal immunity by means of prophylactic inoculations, with the result that adequate circulating antitoxin is available for many years; this basal immunity can be reinforced by a subsequent stimulation.

Ramon and Zoeller (1927) showed that active immunity to tetanus could be established by injections of formol toxoid. This discovery was confirmed in 1938 in the Vaccine Department of the Royal Army Medical College by Major (now Brigadier) Boyd (1938) working with Dr. R. A. O'Brien of the Wellcome Research Laboratories. These experiments proved that inoculation with two doses of 1 ml. of potent tetanus toxoid given at an interval of six weeks established satisfactory basal immunity and produced a concentration of antitoxin in the serum above the level of that believed necessary to confer protection against tetanus. It was also found that neither tetanus toxoid nor toxoid-antitoxin floccules produced a general or local reaction.

As a result of these findings active immunization against tetanus was officially introduced in 1938 in the British Army.

The War of 1939–45: Active Immunization against Tetanus

Active immunization against tetanus was used as a routine measure in the British and American Armies. There were, however, some differences in the technical procedures adopted of which the following illustrate the main features.

Method of Immunization in the British Army (*Boyd*, 1946)

(*a*) From 1938 to January 1941, active immunization against tetanus was by inoculation with two doses of 1 ml. of tetanus toxoid given at intervals of six weeks.

(*b*) In January 1941 a further inoculation was added, making a total of three doses, each at an interval of six weeks.

(*c*) In November 1942 instructions were issued for an annual "boosting" dose of 1 ml. to all troops.

When wounded, any man who had *not been actively immunized* was given three doses of 3,000 international units (1928) of antitoxin at weekly intervals. *Actively immunized* men were given a single dose of 3,000 units as soon as possible after wounding.

Method of Immunization in the United States Army (*Long and Sartwell*, 1947)

(*a*) From 1941 immunization was carried out by giving to all military personnel a series of three subcutaneous injections of 1 ml. of tetanus toxoid at intervals of three weeks. A "routine" stimulating injection of 1 ml. of toxoid was given one year after completion of primary inoculation.

(*b*) From April 1941 until September 1944, when it was discontinued as unnecessary, a stimulating dose of toxoid was given to all individuals on proceeding to a theatre of war, if their departure was more than six months after their primary or last stimulating inoculation.

An "emergency" stimulating dose was given to all personnel who were wounded, severely burned or received other injuries. A dose was also given on the manipulation of old wounds considered to have been potentially contaminated with *Cl. tetani*.

The use of tetanus antitoxin was reserved for treating cases of clinical tetanus and for the passive immunization of non-immunized men with tetanus-prone wounds or injuries.

The noteworthy difference between the procedures adopted by the British and American Forces was that while the British gave tetanus antitoxin on wounding, the Americans gave an "emergency" stimulating dose of tetanus toxoid.

Comparison of the British and American Experiences

The incidence of tetanus in the African and European Theatres has been analysed and discussed by Boyd (1946) and that in the United States Army by Long and Sartwell (1947).

Of the 103 cases of tetanus collected by Boyd, the total number occurring in battle casualties was 35; 18 cases developed in non-battle casualties. The remaining 50 cases were in partisan troops or prisoners of war. Of the 12 cases of tetanus known to have developed in the Army of the United States, only one resulted from a battle wound. Details of the relative incidence, state of protection and mortality are given in Tables I, II and III.

Table I.—Relative Incidence of Tetanus

	No. wounded	Cases of tetanus	Rate per 1,000	
War of 1914–18:				
British Army (Western Front) ..		No antitoxin available		
August–October 1914.. ..	—	—	8·00 (No antitoxin)	
		Prophylactic antitoxin		
Whole war	1,710,369	2,529	1·47	
American Army	523,158	70	0·134	
War of 1939–45:				
British Army—				
African and European Theatres	288,936	35	0·121	
BEF 1939–40	16,193	7	0·43	Basal
BLA 1944–45	103,343	6	0·06	immunity
Total North-West Europe ..	119,536	13	0·11	
American Army	160,254	1	0·0062	

TABLE II.—STATE OF PROTECTION (Deaths in Parenthesis)

	No. cases	Protected	Non-protected	Doubtful
British Army	103 (48)	22 (11)	62 (29)	19 (8)
Battle casualties ..	35 (11)	16 (5)	12 (4)	7 (2)
American Army	12 (5)	6 (3)	6 (2)	—

TABLE III.—MORTALITY RATE IN PROTECTED AND UNPROTECTED CASES

	No. of cases	Deaths	% mortality
1914–18 *Effect of Passive Immunization*			
France 1916–18:			
A.T.S.	520	345	66·3
No A.T.S...	72	60	83·3
England (Sir David Bruce):			
A.T.S.	899	203	22·6
No A.T.S...	559	298	53·3
1939–45 *British Army—Effect of Combined Active and Passive Immunization*			
Actively immunized:			
A.T.S.	11	2	18·2 } 50%
No A.T.S...	11	9	81·8 }
Not Actively Immunized:			
A.T.S.	23	10	43·5
No A.T.S...	39	19	48·7
Incompletely Immunized or doubtful:			
A.T.S.	3	2	66·7
No A.T.S...	15	5	33·3
1942–45 *American Army—Effect of Active Immunization and "Emergency" Booster*			
Actively immunized:			
"Emergency" Booster	4	2	50·0
No "Emergency" Booster	2	1	50·0
Not Actively Immunized:			
A.T.S.	2	1	50·0
No A.T.S...	4	1	25·0

The value of active immunization against tetanus may be assessed from the following observations:

(*a*) Comparing the incidence per thousand on the Western Front during 1914–18 war with that in the BEF 1939–40 and BLA 1944–45, a considerable reduction from the 1914–18 figure to the more recent figures is seen. The incidence in the BEF where men had only their basal immunization by two doses was 0·43 and in the BLA after the introduction of annual boosting doses the incidence fell to as low as 0·06.

(*b*) The extremely low incidence of tetanus in the American Army supports the value of active immunization, particularly when reinforced with regular booster doses and an "emergency" stimulating dose at the time of wounding.

(*c*) The mortality rate for protected men in both the British and American cases of tetanus is the same, i.e. 50% (Table III). But the case mortality rate was lower in the small series of actively immunized men who had also received tetanus antiserum.

Active immunization would certainly appear to be the outstanding factor in the reduction of tetanus to negligible proportions in the British and American Armies during the war of 1939–45.

THE POST-WAR PERIOD

Active immunization was discontinued after the cessation of hostilities in 1945, but as the international situation had deteriorated, was reintroduced in 1949 (September). The object of this was twofold—*firstly* to ensure that troops proceeding to areas of active operations would be adequately protected, and *secondly* to ensure that men would have their basal immunization carried out during their national service, in order to build up a section of the community whose immunity could be readily reinforced by a booster dose of toxoid, should they be required for service in the event of a national emergency.

Instructions were issued that the prophylactic procedures used in the British Army during the last war would be continued as an interim measure. But unless in an area of active operations, reinforcement would be carried out every five years by means of a single booster injection.

There are certain objections to the administration of an antiserum prepared from horses: there is an ever-present risk of reactions due to hypersensitivity, which necessitates taking special precautions that are neither desirable nor always possible under active service conditions, and the unnecessary

tying up of large stocks of antiserum is uneconomical. The results obtained in the American Army by the use of an "emergency" stimulating dose of tetanus toxoid on wounding or injury, appear to indicate that the prophylactic use of tetanus antitoxin is unnecessary in actively immunized subjects.

Boyd (1946) considered that the weightiest argument in favour of antitoxin as opposed to toxoid, was that the former afforded some protection to the non-reactor, the poor reactor, and to those whose circulating antitoxin had dwindled in the course of time, none of whom could gain immediate benefit from a dose of toxoid.

Before reaching a decision as to whether tetanus toxoid or tetanus antiserum should be given to the actively immunized soldier on wounding, the Army Pathology Committee considered it essential that certain investigations should be carried out on volunteers. Once again the assistance of the Wellcome Research Laboratories was sought, and Miss M. Barr kindly agreed to collaborate. She undertook to carry out the numerous antitoxin estimations involved in the investigation and to correlate the findings. Dr. H. J. Parish arranged to prepare a tetanus antitoxin containing 500 I.U. (1950) for use in the investigations.

The instructions for carrying out the different investigations were issued in October 1950. To ensure that random samples were obtained and that too great a load was not put on any particular unit, it was arranged to ask for R.A.M.C. volunteers from the larger hospitals and medical units in the United Kingdom, Middle East and Germany. The response was satisfactory and it was possible to complete nearly all the investigations planned.

These investigations were primarily designed to obtain data on the following points: (*a*) the level of circulating antitoxin in men immunized five or more years ago; (*b*) the effect of reinforcing injections of tetanus toxoid on men previously immunized; and (*c*) the effects of combined active and passive immunization on the titre of circulating antitoxin.

It is difficult to make an accurate assessment of the protective value of the circulating antitoxin, since the level necessary to protect against the development of clinical tetanus is unknown, and would be expected to vary according to the nature and site of the wound. Presumptive evidence may possibly be obtained from the titre of the circulating antitoxin following a prophylactic inoculation. It has been shown that during the war of 1914–18, a single injection of 500 units of antitoxin reduced the incidence of tetanus eightfold.

After an intramuscular injection of refined horse antitoxic serum it has been found that the distribution and subsequent elimination of the antitoxin can be divided into phases:

Phase A when the antitoxin is being distributed: the highest titre is reached in two to four days.

Phase B commences after the third day when there is a steady exponential loss.

Phase C when there may be a rapidly accelerated loss due to precipitin formation in a subject who has received a previous injection or injections of antiserum prepared from the horse. This may commence at any time after the injection. I am indebted to Miss Barr for the figures given in Table IV.

TABLE IV.—THE TITRES OF ANTITOXIN AFTER AN INTRAMUSCULAR INJECTION

	Dose	1500 units	500 units
Phase A	24 hours	0·10 unit	(0·033) unit
	3 days	0·17 „	(0·057) „
Phase B	5 days	0·13 „	0·043 „
	7 days	0·10 „	(0·033) „
	10 days	0·07 „	0·020 „

(The figures in brackets are calculated and not actual figures.)

From the data available about the practical value of a single prophylactic injection of antiserum, it may be presumed that the protective power of a circulating antitoxin titre of 0·1 unit in an actively immunized individual would be at least equal to that of the 0·1 unit expected to be present seven days after a prophylactic injection of antitoxin. This titre will be taken as the baseline when assessing the results of the following investigations.

Investigation to Determine the Titres of Circulating Antitoxin in Subjects who had been Actively Immunized against Tetanus Five or More Years Ago, and who had Since Received Neither Tetanus Toxoid nor Antiserum

During the investigation it was found necessary to widen the scope and include any volunteers with a history of previous immunization. These pre-injection titres form the basis for assessing the effect of the booster dose of toxoid.

The results of this investigation are given in Tables V, VI and VII (the two latter were compiled from data supplied by Miss Barr).

Table V shows a comparison between American figures given by Long and Sartwell (1947) and Baird (1949) and the findings of the present investigation.

From Table V it will be noted that there is relative agreement between British and American figures. In this group of 94 subjects, 19 show a titre of <0·1 unit per ml.—6 out of 31 are British and 13 out of 63 American.

For the one- to five-year group corresponding figures are: British 3 out of 20 and American 10 out of 55. The only subject in the series failing to show the presence of detectable antitoxin was a British soldier. He had received the primary course of two inoculations in 1938 and no subsequent boosting dose until 1949. It would appear that eleven years is too great an interval between primary immunization and the reinforcing dose.

In addition to the 31 men who had received one or more boosting doses of toxoid after the primary course of two injections, there is a further group of 65 men who had received the primary course of two injections only. The pre-injection titres of these two groups are considered in Table VI.

TABLE V.—PRE-INJECTION ANTITOXIN TITRES OF ACTIVELY IMMUNIZED MEN GROUPED ACCORDING TO DATE OF LAST DOSE OF TOXOID

TITRE	PERIOD SINCE LAST DOSE OF TOXOID (YEARS)															
	1 - 3				3 - 4				4 - 5				OVER 5			
	L	B	A		L	B	A		L	B	A		L	B	A	
<0.01	-	-	1	1	-	-	-	-	-	-	-	-	-	-		-
0.01- <0.1	3	-	-	3	-	1	1	2	1	5	1	7	-	3	3	6
0.1 - <0.5	7	-	-	7	5	1	2	8	4	5	1	10	-	3	4	7
0.5 - <1.0	10	-	-	10	4	-	1	5	1	-	2	3	-	-	3	3
1.0 - <5.0	3	-	7	10	2	1	2	5	2	-	1	3	-	2	1	3
>5.0	-	-	1	1	-	-	-	-	-	-	-	-	-	-	-	-

L = Long and Sartwell (1947). B = Baird (1949). A = Army (1951).

TABLE VI.—PRE-INJECTION TITRES OF ANTITOXIN IN GROUPS OF ACTIVELY IMMUNIZED MEN

Titre of Anti-toxin	5-12 months		1-5 years		> 5 years		Total	
	A	B	A	B	A	B	A	B
None detectable	-	8	1	2	-	2	1	12
0.01 - 0.1	-	17	2	11	3	4	5	32
0.1 - 1.0	-	12	6	6	7	2	13	20
> 1.0	-	1	11	-	1	-	12	1
	-	38	20	19	11	8	31	65

Group A: Men who had received one or more booster doses of toxoid.
Group B: Men who received the primary course of two injections only.

These figures emphasize the importance of regular reinforcing doses to increase and maintain a high titre of circulating antitoxin.

The proportion of men with very low titres was unexpectedly higher among those in the five- to twelve-months group than among those immunized one to five years previously. An analysis of the immunization history of men immunized between seven to twelve months previously is given in Table VII.

TABLE VII.—PRE-INJECTION ANTITOXIN TITRES IN A GROUP OF MEN IMMUNIZED 7–12 MONTHS PREVIOUSLY

	Interval between 1st and 2nd Injections	
Titre of Anti-Toxin	Under 6 weeks	6 weeks over
None detectable	4	3
0.01 - 0.1	8	7
0.1 - 0.5	3	6
0.5 - 1.0	-	1
1.0	-	1
	15*	18

* < 21 days 9, and between 21 and 27 days 5.

These findings confirm previous observations made by Boyd (1938) that the most satisfactory interval between the first and second doses of toxoid is six weeks and that unless this interval is adhered to, primary immunization may be unsatisfactory.

From the distribution of the pre-injection titres given in Tables VI and VII, it would appear that a primary course of two injections of tetanus toxoid is insufficient to provide satisfactory protection for the bulk of the population.

Investigation to Determine the Effect of Reinforcing or Booster Doses of Tetanus Toxoid on the Circulating Antitoxin

Volunteers were selected from men receiving their third dose of toxoid after primary immunization by two doses seven to twelve months earlier. A second group was selected from those who had had one or more boosting doses previously, and were due to receive a booster dose of toxoid. Samples of blood were taken before the injection and on the fifth, tenth and 56th days afterwards.

The findings in the main confirm the observations made by the other observers referred to in this paper. From the practical point of view the results can be summarized as follows:

(1) The majority of subjects who had received their primary immunization or a boosting dose within five years showed some measurable response by the fifth day after injection.

(2) The five-day titre might be below 0·1 unit in some men who were given a third dose of toxoid in order to complete their initial course of immunization between seven and twelve months after the two primary injections.

(3) In previously immunized men there is a marked increase in the titre of the circulating antitoxin occurring between the fifth and tenth days after injection. This is considerably greater than that occurring between the time of injection and the fifth day.

(4) There is strong evidence that an unsatisfactory primary course of two injections, e.g. when the interval is shorter than six weeks, might adversely affect the response to the third dose of toxoid. The fifty-sixth-day titres particularly emphasize the unsatisfactory response to a subsequent injection, when the first two doses of toxoid are given at an unduly short interval.

(5) The greater number of stimulating doses received, the more satisfactory and more lasting the immunity produced.

Investigation to Determine the Effects of Combined Active and Passive Immunization on the Titre of Circulating Antitoxin

Two groups of volunteers were required for this investigation:

Group A: Men not previously immunized.—These men were given an injection of 1 ml. tetanus toxoid and 500 units of tetanus antiserum in opposite arms at the same time. A second dose of 1 ml. of tetanus toxoid was injected six weeks later. Blood samples were taken prior to inoculation and on the fifth, eleventh, and fifty-sixth days (i.e. fourteen days after second dose) after the first injection.

Group B: Men with a history of previous immunization.—These men were given, when due, the normal booster dose of 1 ml. of tetanus toxoid and 500 units of tetanus antitoxin in opposite arms at the same time. Blood samples were again taken before the inoculation and on the fifth, eleventh and fifty-sixth days after the injection.

The object of this investigation was to obtain an indication of the response (circulating antitoxin) when wounded men receive both toxoid and antitoxin.

Group A: Men not previously immunized.—Since it had been shown previously that there could be no response to the first injection of toxoid by the eleventh day, it was assumed that the level of circulating antitoxin on the fifth and eleventh days could be regarded as due to the tetanus antitoxin. Of the 26 men in this group 6 showed an accelerated elimination—there was no detectable antitoxin (< 0·005 unit). Omitting these six men the mean titres for the twenty men were:

Five days—0·0544 unit per ml.
Eleven days—0·0250 unit per ml.

None of the men in this group could recall having had previous injections of serum. 3 stated that they had had diphtheria in infancy and it is possible that antitoxin may have been administered then. Of these 3 men one had eliminated all the antitoxin by the eleventh day. No case of serum sickness occurred in this investigation.

The titres of the fifty-six-day samples of this group were compared with controls who had only received the two injections of tetanus toxoid at an interval of six weeks. The comparative findings are given in Table VIII.

TABLE VIII.—ANTITOXIN TITRES OF MEN AFTER PRIMARY IMMUNIZATION

Titres of antitoxin.	500 units antitoxin.	CONTROL (No antitoxin)
0.01 - 0.1	5	-
0.1 - 0.5	7	1
0.5 - 1.0	2	1
> 1.0.	13	22
Total.	27	24

It is evident from this table that the response given by subjects in the group receiving antitoxin is not as satisfactory as the response shown by the controls. It appears that an injection of antitoxin given at the same time as the first injection of tetanus toxoid resulted in some form of interference. This might in part be due to neutralization of the toxoid by antitoxin during and after absorption.

Group B: Men with a previous history of immunization.—This group was intended to be representative of those men who had received an earlier course of active immunization, but in whom circulating antitoxin may be insufficient to afford complete protection and for whom combined active and passive immunization might be used. It was found that by the fifth day, out of 23 subjects in this group, 16 had a definite and significant rise above the pre-injection titre of the circulating antitoxin (these increases being outside the limits of experimental error), *three* showed a probable rise, *three* had no response and *one* showed a slight but definite fall in titre. In this case active interference, due to precipitin formation (assumed), occurred early.

By the tenth day after combined injections of toxoid and antitoxin the passive titre would have fallen considerably, and all men would be expected to show an active response to the stimulus of the toxoid. This in fact did occur, and in the samples taken nine to twelve days after injection, no subject in a group of 27 men had a titre below 1 unit and 18 ranged from 10 to 100 units per ml. Of 5 men with ten-day titres between 1 and 5 units per ml. 3 had received previous serum treatment.

These findings differ from those of the non-immunized group, and would appear to indicate that no inhibitory action would normally be expected to occur from the administration of antitoxin at the same time as toxoid in immunized men.

Observations.—(1) When the results of these investigations are considered it appears that the optimum distribution of antitoxin titres in the majority of the population will be obtained when the following conditions are fulfilled:

(*a*) *The primary course* shall consist of two injections of 1 ml. of tetanus toxoid spaced by not less than six or more than twelve weeks.

(*b*) *The third injection* shall be given between six and twelve months after the second injection.

These three injections are necessary to ensure the development of a satisfactory BASAL IMMUNITY which can be reinforced by means of booster doses. Unless the third injection is given, a primary course of two injections will only ensure satisfactory titres of circulating antitoxin for approximately six months.

(*c*) A reinforcing (booster) dose of 1 ml. of tetanus toxoid shall normally be given every five years to ensure that immunity is maintained. However, when there is a risk of wounding or injury in known tetanus terrain a booster dose shall be given annually.

(*d*) Since it has been shown that the administration of antitoxin at the same time as the first injection interferes with the development of active immunity, any man receiving antitoxin at the same time as his first injection must be completely re-immunized.

(2) It now remains to be considered what further prophylactic treatment, if any, should be given to the wounded or injured man, who has been actively immunized. From the figures given in Tables I, II and III, it can be seen that there was an eightfold reduction in the incidence of tetanus in the British Army during World War I following upon the administration of prophylactic antitetanus serum on wounding. The incidence was further lowered by the use of active and passive prophylaxis in World War II. In the American Army where tetanus toxoid was given on wounding or injury, the incidence was considerably less than that in the British Army.

(3) Before forming any conclusions the facts presented above should be considered in relation to *tetanus prone wounds* and the *incubation period.*

(*a*) *Tetanus prone wounds.*—When wounding occurs in known tetanus terrain, it has been found that the incidence of tetanus is related to the site of injury.

It can be seen from Table IX that the incidence of tetanus is highest in wounds of the lower extremity.

(*b*) *Incubation period.*—In the war of 1914–18, prior to the use of prophylactic antiserum, the peak of the incubation period was on the eleventh day; after the introduction of prophylaxis the incubation period was markedly increased—most cases occurring after the thirty-fifth day. But in the war of 1939–45, the average incubation period in the actively immunized British and American wounded was under ten days. In actively immunized men who had received prophylactic antiserum it was, however, much longer.

The relationship between the elimination of tetanus antitoxin, the response to a booster dose of tetanus toxoid and the incubation period of tetanus are shown in Fig. 1.

(4) From a consideration of the facts outlined above it would appear that most of the evidence is in favour of giving a reinforcing dose of tetanus toxoid in preference to prophylactic antiserum, to the actively immunized wounded or injured man as soon as possible after wounding. This will in future be the policy of the British Army.

(5) The administration of tetanus antitoxin may still be necessary after wounding in known tetanus terrain in the following circumstances:

(*a*) When there is definite evidence of no previous active immunization.

(*b*) Where there are multiple injuries or where there is considerable delay between wounding and surgical attention.

The surgeon first carrying out definitive surgery should decide whether or not antitetanus serum is required.

TABLE IX.—RELATION OF INCIDENCE OF TETANUS TO SITE OF INJURY

	AMERICAN CIVIL WAR		WORLD WAR I				WORLD WAR II		WORLD WAR II	
			BRITISH HOSP. IN FRANCE		HOME HOSPITALS		BRITISH		AMERICAN	
	No	%	No	%	No	%	No	%	No	%
TOTAL CASES	505	-	632	-	880	-	86	-	12	-
MULTIPLE WOUNDS	-	-	284	45	-	-	22	25·6	-	-
SINGLE WOUNDS	505	-	348	55	880	-	64	74·4	-	-
HEAD, NECK, FACE	21	4·1	18	5·1	29	3·3	2	3·1	-	-
TRUNK	55	10·9	66	18·9	135	15·2	6	9·4	1	8·4
UPPER EXTREMITY	137	27·2	76	21·8	236	26·7	14	21·9	3	25·0
LOWER EXTREMITY	292	57·2	188	54·2	480	54·4	42	65·6	8	66·6

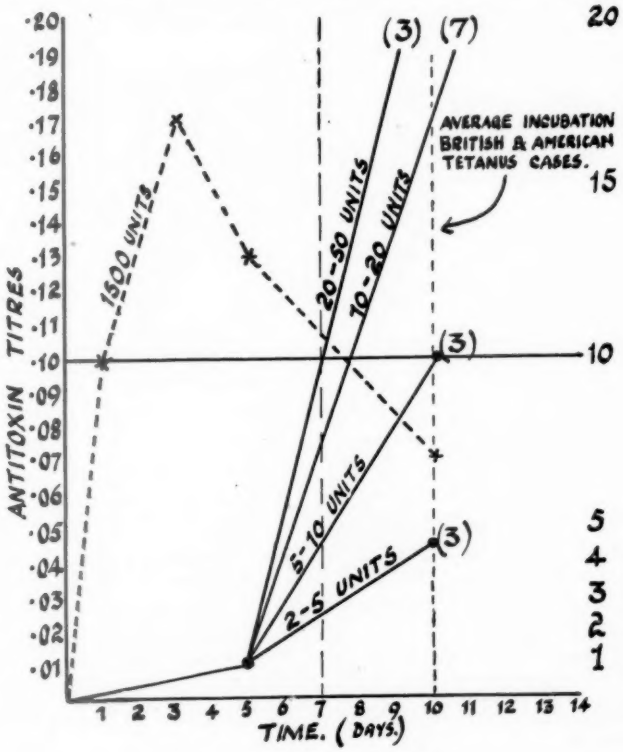

FIG. 1.

---- Excretion of intravenous injection of 1,500 units of tetanus antitoxin.
—— Response of 16 cases to a booster dose of tetanus toxoid.

I must thank those officers who co-operated in the investigation by arranging to give injections and take blood samples, and those officers and men in the R.A.M.C. who acted as volunteers and finally, I must pay especial tribute to Miss M. Barr without whose assistance this investigation would not have been possible and to her assistant Mrs. F. Blackman.

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Brigadier J. S. K. Boyd: Although Brigadier Sachs has covered this subject very fully he has asked me to elaborate two points in rather more detail.

An alum-precipitated toxoid is now used by the U.S.A. forces and it may be asked why we prefer the liquid formol toxoid. The answer is that we know from experience that formol toxoid gives satisfactory and reliable results. It gives no reaction, it is relatively easy to prepare and it is not expensive. Alum-precipitated toxoid is liable to cause local reactions. It is the type of inoculum which might in certain circumstances stimulate the development of a localized poliomyelitis in the same way as does diphtheria A.P.T. The response is slower and it is thus less suitable for administration, instead of antitoxin, when a man is wounded. Finally, it is more difficult to prepare than formol toxoid and hence more expensive. On balance there appear to be no good reasons for making a change, and several for preferring plain formol toxoid.

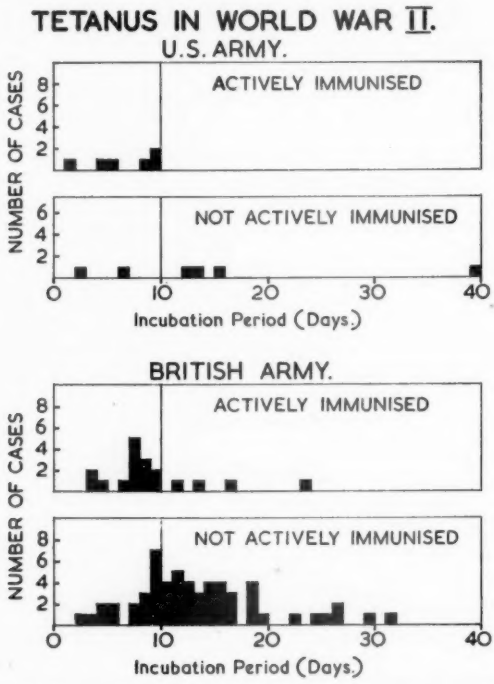

FIG. 1.—The figures from which the graph is constructed are taken from Long and Sartwell (1947) and Boyd (1946). The second part of the graph is reproduced by courtesy of the Editor of the *Lancet*.

During the war it was our policy to give every wounded man a dose of tetanus antitoxin. Our American colleagues, on the other hand, gave tetanus toxoid. The decision to give antitoxin was reached after careful deliberation. It was assumed from the experimental evidence available that a substantial degree of basal immunity would be present in every actively immunized man. This would be stimulated, by the toxin from the tetanus-infected wound, to produce fresh antitoxin which would reach a peak about the tenth day (later experimental work by Zuger *et al.*, 1940 and 1942, confirms that this is so). On the other hand, the initial level of circulating antitoxin, required for immediate protection, might be low. The critical period, therefore,

lay within the first ten days, and this gap could best be covered by antitoxin which affords immediate protection. A dose of toxoid, although likely ultimately to give a higher antitoxin level than would toxin from the wound, provides no additional protection for at least five days. Further reasons for giving antitoxin rather than toxoid were that some wounded men might not be actively immunized—a fact which under battle conditions might well escape notice—and secondly that severely shocked men might not produce antitoxin as rapidly and as freely as the normal volunteers used in the experiment. The U.S.A. authorities based their policy on the assumption that a booster dose of toxoid would give effective protection from about the fifth day. They were doubtful if toxin from the wound would be an effective stimulus.

The incubation periods of reported cases of tetanus in the British and American forces are shown in Fig. 1. These confirm the deduction that the danger period lies in the first ten days after wounding, and show that fulminating tetanus may develop within five days of infection. (It is rather curious that, of the 6 cases of tetanus in actively immunized men in the American Army, only 1 occurred in just under 600,000 battle casualties, while 5 were in non-battle casualties, which must have totalled only a fraction of this number.)

Based on the experience of the war, my personal views on tetanus immunization in the Armed Forces are as follows: (1) Optimum protection is afforded by active immunization reinforced by repeated booster doses of toxoid. The occurrence of a rare fulminating case of tetanus in a community immunized in this way is a risk which cannot be avoided and must be accepted in its proper perspective. (2) Antitoxin is the logical auxiliary protection to offer to the actively immunized wounded man, but routine administration cannot now be regarded as justifiable. (3) Toxoid given to the wounded man can do no harm, will produce enhanced protection after the fifth or sixth day and will do some lasting good by tuning up his active immunity.

I can, therefore, agree with the decision to give toxoid instead of antitoxin to the actively immunized soldier who has been wounded, but only because there is good reason to believe that neither is necessary and because toxoid is readily available and its administration will be of permanent benefit to the man. I still consider that, with the information we had at the begining of the war, the decision then made to give antitoxin was the right one.

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Mr. Harold C. Edwards: As we have been reminded by Brigadier Sachs, tetanus, thanks to preventive medicine, is no longer a scourge; yet it remains a clinical problem of the first order.

Of 31 cases amongst 98,164 wounded U.K. and Commonwealth troops recorded in hospitals during the Italian Campaign, 9 died. A further 22 were recorded amongst other nationalities treated in British Hospitals, of whom 10 died. 11 of those were in Germans, of whom 7 died. Some 80 civilians die annually from the disease in this country. It may be remarked here that a soldier on active service, being protected by immunization, stands a better chance of freedom, and, if attacked, of recovery, than does the unimmunized civilian in total war. The mortality in peacetime is about 50%—though there is some evidence of improvement here. In short, we have an effective preventive, but no effective curative.

A large number of severe wounds sustained in a highly cultivated terrain are contaminated by *B. tetani*. The latter will not necessarily *infect* the wound, however, unless circumstances are propitious for them. Circumstances favourable to bacterial infection and growth are: tension within the tissues due to absence of free egress of the products of injury; impoverished blood supply; dead and devitalized tissue; and the presence of other infections—particularly the *B. welchii*—which will flourish under like conditions. It is the surgeon's role to ablate these unfavourable circumstances, and at the earliest *possible time* after wounding. This time-factor will always be uppermost in the minds of those whose responsibility it is to site Field Surgical Units.

The object of the actual operation—which has been variously called wound excision, wound revision, wound toilet, débridement—is not to sterilize the wound—that would be unreasonable—but to make it unfavourable, even hostile to would-be bacterial invaders. The concept of surgery is *biological rather than bacteriological*. When all is said and done, the best defence against infection is the body's natural response, and the role of surgery is to give those defences a clear field. I stress this point, for there is a danger that what we have learnt in two vast campaigns may be forgotten in this new world, saturated as it is with antibiotics. Whatever changes there may be in antibacterial agents, one thing has never changed—nor ever will change—the reaction of tissues to missile injury. Severe wounds, whether gaping or penetrating, of the fleshy parts, should never be treated by primary suture, either in civilian or military practice, but by a two-stage operation: initial surgery followed in three to four or five days by delayed suture, there being no intervening dressing of the wound. I would particularly like to stress the importance of this.

The initial operation consists of widely opening the wound; excising dead and doubtful tissue; dividing deep fascia to release tension (unbridling or débridement); and leaving the wound gaping wide open, without any packing placed into it; and then putting the part at rest.

One word of surgery in the role of malefactor. There is a danger that late operations on healed wounds, even many years after the infliction, may activate tetanus—and it is, therefore, expedient to give A.T.S. as a preliminary to such operations.

Death in tetanus usually results from the consequences of muscle spasm—not from toxæmia or septicæmia, and recovery is only probable in cases who have been immunized, and in whom, perhaps because of immunization, the incubation period is lengthy.

Antitetanus serum, unfortunately, is of limited value in treatment, for it does not share the toxin's great affinity for nervous tissue. It must, therefore, be given in enormous doses intravenously. The patient must be flooded with it, in the hope that sheer numbers of units will compensate for this lack of specificity. Penicillin is not an antitoxin and is, therefore, powerless to produce any specific action upon the toxin. It should be used in full doses, however, in order (1) to reduce the liability to pneumonia, and (2) to take care of any "fellow travellers"—particularly the *B. welchii* and its associates.

Sir Claude Frankau: For the protection of the civilian population in England and Wales against tetan following injury from bombing precise instructions were issued to the effect that every wounded person to be given as soon as possible an initial dose of 3,000 international units of tetanus antitoxin to be follow by two further similar doses at seven-day intervals—in the event of a wound being septic these two furth doses were to be increased two- or threefold.

Where these instructions were carried out to the letter as far as I know no case of tetanus occurred in air-ra casualties among civilians. I have full records of 7 cases that did occur—2 had had no antitoxin and 5 had ha the initial dose only. Of these cases 4 died and 3 recovered (including 1 to whom no antitoxin had been given

It is probable that a small additional number of cases were not reported owing to destruction of hospita with their records, hurried evacuation of cases and the general turmoil of continuous bombing but I hav no reason to believe that this number was anything but very small. (The total number of wounded civilian was approximately 218,000.)

For British Service patients who had been injected with tetanus toxoid the instructions issued were tha one dose of antitoxin should be given as soon as possible after wounding. In the case of Canadian and U.S.A. troops antitoxin was not to be given but a single boosting dose of 1 c.c. toxoid was to be used instead.

I have records of 6 cases of tetanus in Service cases wounded in Normandy. Of these, 3 had apparently ha full immunization with toxoid, 1 had had no toxoid for two years and 2 had had no toxoid—these latter were Poles. Of these cases all recovered except 1 who was wounded in September 1944 and had not been immunized since November 1942: a single prophylactic dose of antitoxin was given on the day of wounding and tetanus was diagnosed on the ninth day, death occurring forty-eight hours later.

It is not possible to draw definite conclusions from so small a number of cases but it would appear to me that, inasmuch as it would not be possible to immunize the entire civilian population, the proper use of tetanus antitoxin is the preferable method in their case while in disciplined Service personnel the use of toxoid has many advantages.

Surgeon Captain S. G. Rainsford wondered whether it was advisable in view of the advent of such a weapon of warfare as the atomic bomb to propose at this time to abolish the use of antitoxin serum.

The new procedure proposed by the Army depended for its success on an adequate immunological response to a dose of toxoid. For this to happen it would be necessary to make sure that every man had already been rendered basically immune to tetanus toxin, a procedure which it would appear from recent experimental work was not quite as simple as we had imagined and which, to carry out satisfactorily, presented considerable administrative problems and difficulties.

He was surprised to hear Brigadier Boyd state that this secondary response to toxoid might be suppressed by shock and hæmorrhage, since this was quite contrary to the findings of Sir Percival Hartley (1943, 1949). Hartley found that cavies basically immune to diphtheria toxin responded to a stimulating dose of toxoid even when almost moribund. In spite of the findings of Hartley, however, recent work would seem to show that radiation, because of its more selective action on lymphoid tissues and the lymphocyte, might suppress this secondary immunological response. If this should prove to be the case a very serious state of affairs would arise in the treatment of wounded resulting from an atomic catastrophe if no antitoxic serum was available, for it would appear that the only method of preventing tetanus in a wounded man who in addition had been exposed to radiation would be to render him passively immune.

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Mr. A. T. Glenny: Animal experiments have shown that there is a definite inverse correlation between the amount of toxin injected and the time elapsing before symptoms of tetanus appear. Brigadier Boyd's figures showed that the incubation period of cases of tetanus among immunized men was almost always less than ten days while that of many cases among those not immunized was longer. If these incubation periods are translated into amounts of tetanus toxin produced it would appear that most immunized men had sufficient circulating antitoxin to neutralize small amounts of toxin, but some had insufficient antitoxin to deal with larger amounts of toxin. This emphasizes the need for maintaining high antitoxic titres.

Section of General Practice

President—J. D. SIMPSON, M.D., M.R.C.P.

[*May* 21, 1952]

DISCUSSION: CHILD MANAGEMENT

Dr. John Gibbens: My experience of children has been limited to In-patient and Out-patient Hospital work in London, together with a general practice in Kensington for the last twenty years, and a certain amount of consultant work. I have no experience of life and practice in a really poor neighbourhood—no first-hand knowledge of what happens, let us say, in a Welsh mining village, in a depressed area, in the County of Durham, or in a dockside slum. I have had the luck to travel widely in the United States, Canada, Germany, Austria, India, and seen something of the care of children in these countries, but any views based on this experience are bound to be shallow and superficial. I have, however, had certain advantages; I have looked after many children over a long period of their childhood, and had the great advantage of helping my wife to bring up a small daughter, and bringing up your own child teaches you a great deal. Here I would venture to suggest that any views on child management put forward by experts who have never brought up a child of their own should be, shall I say, suspect. Theory is one thing but practice may very well falsify all one's pet ideas.

We are living in an age of revolution when the foundations of everything thought stable and secure are being undermined. Our subject, therefore, is very important and opportune, for on what we believe and teach to-day depends the future generation. Nor can our subject be divorced from the social and political times in which we live. Youth is the main thought of the Russians because they know that control of youth gives them control of the future. We in this country have to make a firm stand for the moral basis of society, for if we decide on a purely materialistic philosophy, we shall surely be submerged before the oncoming tide of Communism.

To bring up a child with a good body is usually simple; to bring up a child with a fine mind is a work of art, very far from easy. I propose to limit my remarks to the training and management of normal children from 1–7.

Is child training and management necessary at all? I am convinced that it is, but there are many child psychiatrists who advise and adopt a policy which is little less than *laissez faire*. Here are quotations from a famous American child psychiatrist and a British professor of child health:

"By the time the child reaches the age of 5 years, one might well suppose that he should know how to eat. In a happy-go-lucky household perhaps he does know, but in another household with exacting standards he falls at least short of expectations. Even when permitted to eat with the family (a mark of promotion), he dawdles, talks too much and he may even ask to be fed. He wriggles in his chair and his napkin must be tucked into his neck to stay anywhere at all. Well, perhaps he will improve in another year, but at the age of 6 he stuffs his mouth, he spills, he masticates grossly, grabs for his food, knocks things over, teeters back in his chair. Besides which, he is reputed to talk altogether too much and kick the table legs. Well, well, perhaps he will improve in another year."

I can only describe this as a policy of no management at meal-times whatsoever. The child has just been allowed to do exactly as he liked, and this is put forward seriously as quite reasonable behaviour for a child of 6–7.

The second quotation:

"The chief essential in the management of a problem is to avoid having a fight with a child, for in fighting over any matter day or night, a child almost invariably wins."

Speaking as a father, I should regard that as a confession of defeat before the battle has begun. I firmly believe that children need guidance, steady training and management, and in this management four things are necessary: kindness, firmness, a sense of humour and willingness to let bygones be bygones. It is not enough to be kind. Firmness and a sense of humour are equally important. In my experience, the reverse is the common failing in mothers—a weak sentimental over-attachment to young children, no firmness and no discipline.

We have all had children brought into our consulting rooms, children who reduce the place to shambles in a few minutes, while their mothers sit by smiling happily. "He is full of life" they say, while he knocks over a vase or spills the ash-tray, while from our point of view the child is an uncontrolled little devil or a perfect nuisance. I am quite certain that children need guidance. They are like rudderless ships, veering this way and that, without any clear direction, and it is our role as parents to keep a firm hand on the tiller.

To change the metaphor: A child born into the world is like a man dropped by parachute in the depths of Tibet or China. He knows nothing of their language, their food and drink, their customs, morals, manners or behaviour. To do well, he needs a firm security and background, and smiling friendly faces around him, but this alone is not enough; he needs to be taught what to do and what not to do, otherwise he will make many mistakes, mistakes which are painful and embarrassing, mistakes perhaps which are dangerous to life or limb. Kindness alone is not enough.

To take a simple illustration—the problem of training a child to be dry at night. All of us see children who at the age of 4 or 5 are still wetting the bed steadily every night. On questioning the mother closely, it is common to find that the child has had no guidance or training. He has had napkins put on him every night and nobody has spoken kindly or sensibly and told him that he was getting too old for such babyish habits, that a wet bed is not right. The mother has just left him in napkins and said nothing, and he has gone on wetting his napkins every night in the simple belief that this was expected of him. To give the child no guidance is to my mind quite unfair. He wants to be told the right thing to do, and he needs to be checked at an early age in any conduct we consider wrong. "Begin as you mean to go on" should be the motto for all parents, bearing in mind that the child should be ripe for any advancement. Many mistakes are due to mistiming our efforts. If a child sits up in his high chair for his dinner, and throws his food all over the ground, he should be told firmly and sharply that this is a disgusting trick and that you will not stand for it. Any more of that nonsense and he can go away and play by himself. He can come back when he is better. Ah, but the mother will exclaim—"Doctor, surely he is far too young to understand". Surely this is not so. A child of 9–12 months understands far more than we are apt to believe. He knows perfectly well by the tone of the voice if his behaviour is thought reasonable or unreasonable. Of course he will throw his food on the ground again, just to see what happens, and if you take the firm line again and stop him doing it, he will try weeping, rage, arching himself backwards, and so forth. Are you, at this stage, to adopt the Professor's advice—"avoid having a fight with a child, for in a fight over any matter the child almost invariably wins"? Certainly not. The fight is on, and if you stand firmly by your guns and flatly refuse to let him go on throwing his food on the ground, the battle will be over very soon. Let him leave his meal and leave the room, and if he bellows with rage, let him do so in an empty room. He will soon give this up for there is no fun in playing to an empty stage. This is far better than allowing him to persist with the bad habit for weeks or months, with all the mess and nuisance it involves, only to scold him at a later date. Once a bad habit is ingrained, it is much more difficult to uproot, and then both the mother and child have a bad time of it. "Begin as you mean to go on." Check every bad habit the first time you meet it, and every time subsequently, and encourage all good behaviour by praise.

Here, I can imagine a shudder passes through the ranks of the psychiatrists—surely this is repression, that overwhelming force we have been taught does so much trouble to the child's ego. I must state my firm belief that psychological jargon has done considerable harm.

Who should be responsible for the child's management? There are several interested people—the mother and father, the nanny, the day nursery authorities, the child guidance clinic, and child psychiatrist. I am told that in the U.S. to-day, many children are taken to a child psychiatrist as regularly as they are taken to a doctor at a Welfare Centre here. Has this proved to be of any great advantage? From what I have seen of American children in the United States and in England, I should very much doubt it. May I quote now from a woman psychiatrist?

"The nurse handed the little girl, aged 4½, over to me and went away, in spite of her tears and screams. I sat at the toy table and began to play by myself. I put the doll to sleep and told the child I was

going to give it something to eat and asked her what it should be. She interrupted her screams to answer 'Milk'. I noticed she made a movement towards her mouth with her two fingers which she had a habit of sucking before going to sleep. I laid her down on a sofa and at her request put a rug over her. She was still very pale and her eyes were shut but she was visibly calmer and had stopped crying. Meanwhile I went on playing with the dolls. As I was putting a wet sponge beside one of them, as she had done, she burst out crying again and screamed—'No, she mustn't have the big sponge—that's not for children, that's for grown-ups'. I now interpreted this material in connexion with her protest against the big sponge (which represented her father's penis). I showed her in every detail how she envied and hated her mother because the latter had incorporated her father's penis during coitus, and how she wanted to steal his penis and the children out of the mother's inside and kill the mother."

From observation of many children, including my own daughter, I should have thought that children were intensely practical, highly receptive and suggestible, and that explanations given by any responsible adult, including psychiatrists, would be swallowed whole. But, do we want interpretations of this sort? Can we be sure that the psychiatrist was not merely projecting her private feelings upon a submissive and receptive child? Cannot harm be done by such interpretations? Surely the responsibility for child management should rest with the mother, and, to a less extent, with the father. I dislike entrusting a child's future to a nanny, though we all recognize that some nannies are excellent and some are indispensable. I look forward to the day when every mother, from the highest in the land to the lowest, runs her first baby single-handed for the first year of his life. I look forward to the time when no mother works in a factory for the first year after the birth of her baby, but learns to bring up her child decently, honourably and sensibly. If after this she wishes to go back to public life or take up a job, she will at least have learned enough to exercise wise supervision over a nanny. Two women looking after one baby is not a good principle. I dislike divided responsibility. Who is to blame if the child grows up badly trained?

I have had to hold the balance between mothers and nurses, and I can only say that Ulysses' task of steering his ship between Scylla and Charybdis was child's play in comparison with this hazardous and dangerous course.

The management of normal children calls for a steady background of love and attention and understanding, and I find it difficult to see how the best run Day Nursery can supply this. Day Nurseries are the product of the queer times in which we live. If, in our philosophy of life, we think it right and proper for a married woman with a young baby to go out to work, there must be Day Nurseries, but at the risk of being thought old-fashioned and reactionary, I do not think they are a happy sign of the times.

Surely it is a mother's job to manage her own child. Grandparents, relatives, nannies, nurses in Day Nurseries, however good they may be, are all second best. We are all familiar with the troubles that occur in broken homes where the mother perhaps goes out to work all day and the father is never there. To quote a Professor of Education: "All through school and for years after school, parents continue to teach their children. They do so, whether they want to or not. The father who never says more than 'Hallo' to his son, and goes out to the pub every evening, is teaching the boy just as emphatically as if he were standing over him with a strap. He may not be teaching his son to drink and neglect responsibilities. The boy may turn out to be a thinking ascetic devoted to long plans and hard work, like Bernard Shaw or Joyce, but for good or ill, the father is teaching him something. Many fathers either do not know this or do not care, yet it is impossible to have children without teaching them. Beat them, coddle them, ignore them, force-feed them, shun them or worry about them, love them or hate them, you are still teaching them something all the time."

Apart from home life, there are four great influences that leave their mark on a child's mind to-day: literature and the press, the cinema, the radio and television; if we are to manage our children wisely we must see that these are suitable to their years. A scarlet thread of violence runs through many films and television scenes, and many so-called comic papers are full of guns and gangsters, not at all suitable fodder for the minds of young children. Children have a wonderful freshness and sparkle about them; a great sense of adventure and fun, and it seems a great pity to let these "trailing clouds of glory" be dissipated too soon. The ugly side of life is bound to come their way one day. Is it not better to postpone it for a few years? To bring up a child in cotton-wool, keeping him out of all contact with the grim realities of life, is a mistake, but is not the ultra-sophistication of modern youth equally deplorable? I am all in favour of going slow and allowing the mind and emotions to unfold quietly, and the better the child's brain, the more unhurried should be the pace. It is a pity to scamper through childhood—"the finest timber is of tardy growth". Radio and television have obviously enormous powers for good and evil. They and the cinema, rather than books and papers, are modifying our children's lives profoundly, and it is clear that we shall have to think very hard what the long-term results are likely to be. Already it seems that the spirit of adventure, the romance of everyday life, the fun of finding out things for oneself, climbing trees, exploring rivers, fishing for tadpoles and all the pleasures of the countryside, are giving place to the nightly sessions in the dark in front of a television screen. Is this a step forward?

One of the major sources of trouble to-day seems to be the horrifying housing conditions with which many parents have to contend. How can a mother manage her child properly if she is living with her in-laws? How can she manage to train her child in a tiny flat where every sound echoes round to her neighbours? How can a mother, father and four children live in two rooms for five years and not be harassed and irritable? What, too, of the hundreds and thousands of D.P.s living in the reception camps of Germany and Austria? What of the thousands of Africans and Indians running wild like animals in the appalling slums that fester around the edges of large cities? The child has no home, a background only of unrelieved squalor and gloom, and he grows up an easy prey of gangsterism and graft, the great scourges of city life leading to cynicism, ignorance, spite and envy.

The impossibility of finding a suitable home in early marriage plays a large part in the enormous illegitimacy rate. It undoubtedly causes much unhappiness when young married couples are forced to live with their parents or parents-in-law, or have to exist in communal rest centres which are anything but restful. In "A Woman at Scotland Yard," Miss Lilian Wyles has given a vivid picture of the evils of slum life, and Miss Marjorie Fry comments: "There is no doubt that absence of a secure and happy home life is the main cause of delinquency and crime."

We have seen what happens when disruption of a family and loyalty to that modern Moloch, the State, becomes the first principle of tyrants in this age of barbarism. All dictators do their best to weaken the ties of home.

What do we want our children to become? Surely the aim of all education and management is the development of *character*. It is not enough to bring up a child with a well-made body and lively intellect. Our late enemies, Hitler, Himmler, Goering and Mussolini clearly had both, yet it did not prevent them from plunging the world into the most devastating of all wars. Character is our aim, so perhaps it is worth while to pause for a moment, to ask ourselves what are the desirable traits in a child's character?

I would put first on my list, courage, moral as well as physical, and as a close second, sensitivity—sensitivity to the moods and feeling and sufferings of others, which is the very antithesis to cruelty and brutality. Much real education can be done by talking to the child as she plays with her dolls; much can be done by talking to a child as you walk along the street. I would not have my child scoff at a beggar or at decrepit old age, nor be cruel to animals. I would teach her to know pain and suffering when she sees them; to have a lively sense of sympathy for others less fortunate than herself.

Other traits I would attempt to foster are truthfulness, honesty, a sense of justice and fair play. Petty pilfering goes on to-day on an enormous scale ; a child should be clearly taught what is his and what is not his. Another important trait is perseverance; the ability to finish a job properly and not to be discouraged at failure at the first attempt; not to scamp work; and here might I quote to you the fine prayer of Sir Francis Drake, written in 1587—"O Lord God, when thou givest to thy servants to endeavour any great matter, grant us also to know that it is not the beginning but the continuing of the same until it be thoroughly finished, which yieldeth the glory; through Him, that for the finish of Thy work, laid down His life: Our Redeemer!"

Last on my list of virtues I would put natural gaiety, a spirit of fun, a sense of adventure, self-reliance and good manners. Civilized life is no longer stable. The future is dark so we must teach our children to adapt themselves to novel conditions. The ugly qualities of the human mind—greed, gluttony, vanity and pride, lying, brutality, cruelty, hatred, jealousy, bad temper, laziness, faint-heartedness—these I would always attempt to quash. This is not "repressing the child's ego". I have little patience with the catchword phrase "A child can do no wrong", which is opposed to all common sense and clinical observation. Surely a child grows up far happier, far more fit to take his place in the world, far less liable to neurosis, if he is given a clear guidance in the way he should go.

Dr. E. Beresford Davies: At the outset I must protest that though I am a psychiatrist I have managed to become the father of three children, no doubt something of a nine days' wonder in view of the previous speaker's revelations about psychiatrists and their work.

There are large groups of nervously sick or impaired children whose care must be in the hands of specialists and who require the environment of specialized institutions: it is possible that, as recognition and provision improve, larger numbers of children will be cared for in this way. Similarly, many children are grossly abnormal from birth or as the result of very early injury and disease: these, too, I am not considering in my present remarks. There remain, however, an equally large group of nervous children who do not go to an institution or spend any long period of time in hospital, but who require management and treatment in their homes and who are properly under the care of a general practitioner. Of this group which is composed of many heterogeneous elements I am choosing mainly two types of children: I cannot give, in the time at my disposal, any adequate account of them and so I propose rather to make a series of remarks as simply and concisely as I can, and hope that the virtue of this method will compensate for its undoubtedly dogmatic presentation.

The two types are, first, the child with a neurotic illness; and, second, the child with a behaviour disorder proper: naturally there is no perfectly clear-cut line between these two. In addition there are mixed types, and children who show neurotic or delinquent trends as a result of some other ailment. By and large, however, this is a useful distinction, and diagnosis is of the greatest importance not only in the definition of the problem but as a guide to treatment and prognosis. I think there is a danger that psychological treatment may be applied too loosely to-day and without a sufficiently clear idea of its aim, so that disorders which require a perfectly well-recognized scheme of handling are dealt with in an unsystematic and correspondingly unsuccessful way.

What briefly is a neurotic child? We do not need to be Freudians to understand that neurosis in this sense is the manifestation of apparently purposeless nervous behaviour accompanied by unsuitable or excessive emotion—of which a component is always fear, whether conscious or unconscious—due to environmental demands upon the child which he cannot meet, for the time being or permanently. It is one of the great diseases of culture and it accompanies forced delay of maturation. Typically the neurotic child shows emotional disturbance, fear, restlessness, alteration in sleep, faulty habits, shyness, stammer, enuresis or somatic symptoms based upon anxiety: of course this list is not intended to be exhaustive. Symptoms may arise in definite form very early, say at 2 or 3, but very often they are minimized or hidden by the parents until school age, when they make themselves obvious. One thinks of bed-wetting at boarding school, the persistence of exaggerated terrors after the first few days as a new boy or girl, failure to associate adequately with other children or the reappearance of aches and pains at first precipitated by some mild and transient physical trouble. I think that school finds out weakness to the greatest extent at the two extremes of the social scale: among the materially fortunate by exposing the spiritual or emotional poverty of the home, and among the underprivileged by demanding standards for which the child is unprepared by endowment and training.

The child with a behaviour disorder, but without psychosis or gross nervous or physical defect, usually shows delinquent trends though they may be mild and confined to disturbance within only a small part of the environment. I would define delinquent behaviour as behaviour in reaction against organized society to the direct detriment of society. I might interpolate here that neurotic behaviour, though also a reaction against society, is chiefly characterized by the suffering of the neurotic individual and only indirectly by the suffering of society.

Delinquency, therefore, according to the circumstances, may be anything from bed-wetting to murder: in fact in this country it consists surprisingly often, in the developed case, of a series of offences against property, with some degree of violence against the person. However, abnormal activity may be no more than misbehaviour or "buffoonery". Its true importance must be judged by its effect on function and the disorganization it causes in the environment. It is distinct from the periodic "breaking-out", known and licensed, particularly at a later age, in modern day university saturnalia, in that it shows no periodicity and is not satisfied by the commission of an act or even a series of them. It seems clearly to be substitutive behaviour, that is behaviour which expresses what is normally shown in other ways. We should expect the young delinquent to show absence of normal expression and indeed he does, just like the neurotic, but in different ways. The delinquent shrinks from competitive contact but invents his own rules: he rationalizes his failures by criticizing the normal: and he is without community or fellow-feeling though his demands for satisfaction from the community are greater than normal. He is apt to live a life of fantasied exploits and thus he never achieves what the genuine rebel may achieve; that is, a genuine revolution with positive qualities of its own.

Of recent years there has been an increasing proportion of cases in which abnormal EEG tracings have been found. The most obvious reason is naturally the availability of the apparatus itself. The interesting fact to me is the frequency of abnormal findings in certain kinds of children who present with behaviour disorder. The abnormality is quite often of epileptic type: the tracing may serve to differentiate such cases very usefully from others so like them clinically. I have supposed that sooner or later such children, if left alone, would have their first fit in early adult life; there are, as far as I know, no grounds for supposing that the progress of the disease can be influenced, but there is no doubt whatever that early medication and supervision does much to mitigate the results of the disease and delay the onset of secondary psychic change. It is probably justifiable to ask for an EEG examination with findings such as ineffectiveness of even severe punishment, the eccentricity of parents or sibs, or the discovery of many "red herrings" in the history, or, more obviously, a family history of epilepsy or allied complaint. The child with a psychopathic type of disorder, though perhaps largely uninfluenced in a favourable way by punishment in the long run, nevertheless usually shows a respect for it and an immediate emotional reaction—other than fury—to it.

What are the salient features of treatment of the neurotic child or the child with a behaviour disorder? Fortunately they are much the same as far as approach and method are concerned. The essence of the approach is the establishment of transference, which is simply effective emotional contact. In the first instance it must be between the patient and the responsible doctor, but later it may be very well developed through a third party, such as a social worker, a speech therapist, a school-teacher or a member of a religious or social group: the responsible doctor then remains in the background

as adviser and "court of appeal". This relationship of patient, therapist and doctor works very well with children, but this need occasion no surprise if we remember the hierarchical structure of the family unit and, in larger terms, the outside world. It even works when one is dealing with the older delinquent, if skilful use is made of his immaturity until such time as he is ready to lose his dependence and hence his transference.

The means whereby transference in younger children may be begun and fostered is through activity by the child such as writing, drawing, painting and playing. I put playing last in the hope of emphasizing that methods other than the classical type of play therapy with its suggestion of experts may be just as effective. At all events young children need a symbolic medium in which to express themselves: they do not have the experience or the emotional power to explain their fears or think in abstract terms. The therapy should at all times be kept at a natural, easy level and I think it particularly important in the average case not to give an impression of extraordinariness or to bribe with material things. Emotional repayment for services rendered is the natural currency, and it should never be forgotten when one is dealing with delinquents. Sudden, dramatic, or "miraculous" cures are usually dangerous failures in neurosis, and, in delinquency, dangerous self-deceptions.

Psychiatric methods are usually and rightly regarded as time-consuming: but they are not so protracted that ordinary doctors in their busy lives cannot practise them successfully. Even five minutes spent weekly by a busy general practitioner has been shown to be a real help and therapeutically effective. Naturally ten minutes is better, twenty are reasonable, and forty or sixty are riches.

It is important to assess the parents before one makes any plan of treatment: one may have to "sort them out" before one can expend any time at all profitably on the child. In a personal case which I first came upon two years ago, I have treated the mother by a more or less classical analytical method, and I have found that there is now no need to treat the three of her five children who were disordered to a considerable extent. It is always reasonable to look for disorder in one or both parents of the child patient: if the parents are not causally connected with the child's psychological illness, they very soon develop a disorder in consequence of it. One must also realize that a vicious circle is easily established in the child as well: the nervously sick child who meets with misunderstanding of his primary manifestations of illness by his parents, sooner or later shows secondary complications.

Unfortunately there are parents who rule by fear: sometimes they adopt it as a policy—sometimes they have learnt it from their own parents. I think the results are almost uniformly unhappy. Fear is the basic emotion of neurosis: it is also I suppose necessary to life, but the dividing line between what is necessary and what is harmful is a very narrow one. Incongruity of the teaching at home and at school causes fear, particularly if the field of difference is the sexual one. It is wrong to send a child to school in such ignorance that it cannot look after itself: it is still worse to send it with wrong information, but this is still happening every day. At a school I know very well the parents are sent a carefully worded letter before their son's first term. One such boy later fell seriously ill and I asked his mother how he could have been so unprotected sexually as he evidently had been, in view of this letter of which I knew. She replied "That filthy document! I burnt it".

As a last word may I suggest that parents sometimes need a holiday away from their psychologically sick children: it does happen that one can leave the child and help the mother to great advantage.

Dr. Alan Maberly: There are three important principles in child management. First the principle of growth and *maturation*. If the child is to develop at the optimum rate, he requires the maximal stimulus to which he can respond in terms of physical, intellectual and emotional development at any one time. No two children develop in the same way, or at the same rate. There should be guiding principles, but no rigid rules, as every child is a unique individual who should be handled as such. Differences and defects in physical development are easy to detect, measure and correct, but in the intellectual, and still more in the emotional, fields, matters are not so easy. Much harm is done by forcing the pace too far and too fast, and the effects may be seen as often in minor physical disability as in psychological disturbance.

Secondly comes the principle of adequate *security* provided by proper physical care and loving protection in the setting of family life. For the latter there is no really satisfactory substitute, and in it both parents should make an equal and complementary contribution, not in conflict, but in balance. Where the mother is protective, tender and cautious, the father should be tough, adventurous and outgoing. In a Welfare State with its matriarchal character, its emphasis on security, sickness and safety, and its distaste for effort and discomfort and the other normal accompaniments of masculine striving and achievements, it is more than ever necessary that fathers should assert themselves. If home life is satisfactory and satisfying, behaviour disorders and problems of discipline and of control rarely occur. Where parents are in conflict the children take sides or lose all sense of security and suffer accordingly.

Thirdly is the problem of *consistency*, with frankness and honesty between the parents and the children and between each other. Very many problems arise because there is inconsistent handling,

as between the parents or between one time and another. It should not, however, be forgotten that all children put their parents on pedestals and regard them as omniscient and omnipotent, even while they see through insincerities, and irrespective of what the parents themselves say or do. The breakdown of the illusion in adolescence is normal and an inevitable part of growing up.

The family doctor plays a big part in maintaining the child's sense of security. When illness strikes, the wisest of parents may become puzzled, uncertain and anxious, at a loss what to do next. The doctor can bring about an authoritative reassertion of confidence and certainty. In minor behaviour disorders, as in minor ailments, he should be the first line of defence, someone to whom parents turn for advice and guidance long before it is necessary to seek help from the specialist services in clinic or hospital.

Dr. Ronald Mac Keith: I notice that the persons usually consulted on child management are neighbours, relations and perhaps nurses. The puerperium offers a moment of receptivity and I recommend Spock's little book on child care[1], as almost ideal for the mothers to fly to.

For one group of mismanagers doctors must partly take the blame. This is the group of over-anxious, uncertain people who have been persuaded that bringing up children is very difficult and liable to end in disaster. It is wise to flatter these parents and restore their self-confidence, for children are resilient and likely to turn out well.

Dr. E. M. Dimock: From my experience as a family doctor working in a community, I would place the emphasis on the doctor's attitude in child management, starting at the first ante-natal consultation for the first child. In the ante-natal period the doctor meets the family on predominantly health grounds; disease and abnormality are relegated to the background. The ante-natal consultations together with those in early infancy set the tone for mutual consideration by doctor and parents of any future problems in child management.

When Dr. Gibbens suggests that certain misdemeanours should be checked every time, he speaks like a man. Too large a share of the upbringing of children is borne by the mother, maternal fatigue is one of the main stress syndromes of our civilization. The father should play his part not only in providing the firmness required in child management rightly stressed by Dr. Gibbens, but should take other steps to avoid maternal fatigue. For instance by providing a "sitter-in" he may insist on the mother escaping from the home for a few hours to become a wife once a week.

Dr. David Morris: Children are taken to the doctor when things have gone so wrong that the parents are disturbed and feel the need for help and advice. Emotional disorders account for a great deal of children's symptoms and doctors and parents are learning more and more about children's development. Parenthood is an exacting speciality; a sympathetic attitude to the parents goes a long way in helping them to cope. By attempting to deal with the problems much is learnt in the process and a surprising amount of useful help given. The preventive side offers the greatest potential for activity: talks at mothers' clubs in ante-natal departments, small group discussions in infant welfare clinics, attempts by health visitor, practitioner and pædiatrician to grapple with the minor trivial disturbance before it becomes more serious or deep-rooted—all these are important in helping parents and children psychologically.

Dr. Lindsey Batten: Only citizens of the highest quality can maintain a "Welfare State". How much upbringing can effect is another matter. A great part of physical, intellectual and mental health and capacity depends on the "luck of the draw" and I think more reasoned fatalism would be good for us all. Upbringing can be overdone, witness the poise and good manners of at least some children left largely to bring up themselves. I prefer flexibility to firmness in dealing with the refractory infant and I think obedience can best be secured by foreseeing and by-passing the head-on collision. Example is better than precept and parents who provide food, shelter, clothes, space, and especially brothers and sisters, play with their children, teach no fear and show respect for truth, beauty, kindness and courage, can sit down feeling they have done their duty.

Dr. M. C. Andrews: The Arab child grows up blissfully without any prohibitions: yet the modern Arab is hardly the type we aim at producing.

Parental example is the basis of a child's upbringing: but example sometimes needs explanation, because the child has insufficient background to interpret example. Too many parents shrug their shoulders and say, "Leave it till he goes to school."

"Don'ts" in the home should be reduced to a minimum: but the child should learn that "don't" means "*do not*" and nothing else.

Housing difficulties are not an excuse for one-child families. The whole of an anxious mother's love and a father's pride is too great a burden for one small child.

[1] SPOCK, B. (1946) Pocket Book of Baby and Child Care. New York and London.

Dr. E. P. Scott: No speaker has mentioned the subject of corporal punishment in the management of children.

The whole discourse has apparently been centred on psychiatric methods. I would have liked to hear the views of a pædiatric specialist.

Please do not think for one moment that I am referring to punishment for the abnormal child—far from it—my remarks concern the ordinary healthy youngsters who make up, happily, the largest proportion of our children. I cannot see what is wrong with just and healthy chastisement. It alters neither a child's respect nor affection for his parents, nor does it alienate them, in fact it does the reverse—it increases these feelings—as we all know in later years. This also applies to one's life at school.

There appears to have been a great increase in recent years of criminal tendencies and delinquency in children, and I cannot help feeling that though war may have played a part, it is mostly due to lack of parental discipline and correction. The normal child tends to recognize corporal correction if administered justly and at once, and bears no rancour.

Dr. Walter Hedgcock: Considerable stress has been placed on normality and abnormality in child and/or parents, but so far there has been no mention of normal child and normal parents—but an abnormal relationship. The main example of this, an increasing modern problem, is when a childless couple adopts a baby. This always produces problems in the management of the adopted child.

I think guidance is needed particularly on the very difficult question "when should the child be told that his present parents are not his natural parents?"

Dr. Guy Daynes: Many get the false impression from psychiatric teaching that any form of fear in the nursery is wholly bad. Experiences that frighten some children are greatly enjoyed by others, and indeed even enjoyed by the timid ones when they are older. Fear is a dominant emotion throughout life, and children should not be protected from it but gently accustomed to it, thereby facing it for themselves and deriving satisfaction from having done so.

Dr. J. J. Kempton: There are a large number of behaviour problems to be seen in the pædiatric out-patient department. I recall the words of Dr. Hector Cameron, who observed that the child tries to live up to what it believes to be its reputation. The mother gives a long account of how the child refuses to eat, refuses to sleep, and so on, the child meanwhile sitting by her with a look of approval on his face. There can be too much management, and certainly too much talk about management.

Section of Neurology

President—Professor P. C. P. Cloake, M.D., F.R.C.P.

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DISCUSSION: RECENT WORK ON THE PERIPHERAL NEUROPATHIES

Dr. J. St.C. Elkington: The phrase "peripheral neuropathy" is a comparatively recent recruit to medical literature. It may be said to comprise that group of disorders previously referred to as "peripheral neuritis", "polyneuritis", "multiple neuritis", or "symmetrical peripheral neuritis" on the one hand and the different varieties of "neuritis" of individual peripheral nerves on the other. The phrase has certain advantages. In addition to providing a convenient common name for these two groups of conditions, it has the advantage of avoiding the suggestion that they are inflammatory in nature for we now know that the majority of them are not. To define the term "recent" is more difficult, particularly in a subject where the growth of knowledge has been continuous for many years but it has seemed to me that a period of thirty years would be a convenient one, as this covers the era of modern biochemistry as applied to clinical medicine and of the growth of our knowledge of vitamins.

Sir William Gowers (1892) was much in advance of his time. He drew a clear distinction between "multiple neuritis", or "polyneuritis" on the one hand and isolated "neuritis" of one or more peripheral nerves on the other. In the former, "multiplicity is its most obtrusive symptom"; "it is characterized by its symmetry and is due to a morbid blood state having a direct influence on the nerve tissues"; "its cause is the presence in the blood of some virus, often an organic, or inorganic chemical compound to which the nerve fibres are susceptible, just as they are susceptible to curara". In the latter, "the connective tissue and especially the sheath of the nerve is the part primarily affected, and the nerve fibres are damaged only in a secondary manner". This subdivision of peripheral neuropathies remains valid to-day and will be adhered to in this review. It is with the first group that I shall principally be concerned.

After reading Gowers' account of multiple neuritis, it is clear that it is not on the descriptive clinical aspect of the subject that advance is to be looked for. Few of us have seen as much polyneuritis as he and fewer still can rival his powers of description. The advance in our knowledge of this condition in the past thirty years is to be found rather in two different directions, namely:

(*a*) A change in our conception of the pathology of the condition and the substitution of a chemical and even a physical concept for a structural concept as to the essential cause of the condition. In other words a movement from a static to a dynamic viewpoint.

(*b*) A widening of our knowledge of its causes.

A Change in Outlook

Morbid anatomy and histology have given little help in solving the problems of polyneuritis. This statement implies no criticism of these methods in themselves, but they are not capable of solving the essential problem of why the nerve fibre ceases to function. Numerous examinations both during life and after death have demonstrated that in cases of chronic polyneuritis the nerves show degeneration of the axones, a breakdown in the myelin sheaths, changes in the neurilemma and proliferation of the interstitial fibrous tissue. In more acute cases the changes are confined to swelling of the axones together with chromatolysis and nuclear changes in the corresponding nerve cells. These changes are non-specific and can be seen in their full range in many different varieties of polyneuritis, the details depending upon the intensity and duration of the disease, rather than upon its cause. Such histological studies tell us no more about the true nature of the disorder than sections of the heart valves in mitral stenosis tell us about the nature of acute rheumatism. No one who has watched a case of "infective polyneuritis" varying in intensity from day to day and almost from hour to hour, or has seen a case of acute porphyria overwhelmed and dying of universal paralysis within a day or two of the first symptom can doubt that we are here dealing with a disorder of function whose explanation is to be sought in terms of biochemistry rather than of morbid anatomy.

A brief examination of the processes known to be involved in the activation of muscles and glands by impulses transmitted down the peripheral nerves may be of value in indicating some of the ways in which this process may break down.

The process whereby the nerve impulse is transmitted along a nerve fibre is now generally accepted as being electrical in nature. It depends upon the passage of a self-propagating wave of altered permeability down the nerve-fibre membrane which separates the axoplasm with its high concentration of potassium ions from the extracellular saline medium with its high concentration of sodium ions. This delicate system can only function if the concentrations of potassium ions in the axoplasm and of sodium ions in the extracellular fluid are maintained within certain limits. In extreme disorders of electrolyte metabolism nerve conduction is impaired or lost. This seems to provide a possible explanation of the cases of paralysis that may occur in the terminal stages of renal disease and Addison's disease.

It is known, too, that the maintenance of sodium and potassium equilibrium across the cell membrane involves the continuous expenditure of minute amounts of energy and that the passage of the nerve impulse is associated with the liberation of heat. As far as is known the only source of energy available to nerve tissue is the metabolism of carbohydrate. It might therefore be expected that some connexion would exist between nerve conduction and carbohydrate metabolism—an aspect of the subject which will be dealt with by Professor Thompson.

The transmission of the impulse from the nerve fibre to the effector organ—either muscle or gland—is brought about by the liberation of a pharmacologically active substance, acetylcholine, adrenaline, or some allied substance. This, in its turn, is immediately removed by the action of an appropriate enzyme. This complicated mechanism of transmission provides several opportunities for breakdown. The activating substance may be liberated in insufficient amounts; its action may be blocked by the presence of some chemically allied substance of greater stability or the enzyme system may be impaired or destroyed by some inimical chemical agent. Such processes are known to underlie examples of what we may call "acute experimental neuropathy" such as poisoning by curare, methonium compounds and fluorophosphate compounds. Not all of them have yet been proved to take place in naturally occurring polyneuritis.

So far my remarks on the transmission of the nervous impulse have been concerned with efferent impulses. There is every reason to suppose that the process of transmission of the impulse up an afferent nerve is essentially the same as that of transmission down an efferent one and is liable to the same disorders. But little is yet known as to what happens at the peripheral sensory end-organ whose function it is to lower the threshold of the nerve to a specific form of sensory stimulus. This will need to be unravelled before polyneuritis can be fully understood for one of its most puzzling features is the extent to which its effects may be selective, involving predominantly either motor or sensory functions, or picking out one aspect of sensation and sparing others. An equally puzzling feature is what may be referred to as "regional specificity" seen in many cases of peripheral neuropathy. We do not know why the nerve elements in the distal parts of the limbs are so commonly affected first in many varieties of peripheral neuritis. Their distance from their cell bodies seems an inadequate explanation. Indeed in many cases of so-called "infective polyneuritis" it is the proximal muscle groups that are first involved. Again, why should botulinus toxin absorbed from the intestine have a selective action on the nerve fibres or cells innervating the bulbar muscles. Why should Stilbamidine have a special affinity for the sensory fibres of the trigeminal nerves, or streptomycin for those of the vestibular and cochlear nerves?

Widening Knowledge of Ætiology

Our views on the ætiology of polyneuritis are changing. Gowers stated that all cases of multiple neuritis were due to the presence of some alteration in the circulating blood which had an adverse effect on the nerve elements. Even in his day, many toxic agents were recognized such as metallic poisons, diabetes and bacterial toxins, but in many cases the cause remained obscure. To-day it is still true that in many cases no exact cause can be determined. I have looked through the notes of 34 cases of multiple neuritis admitted to the National Hospital, Queen Square, in the past four years. Of these, the cause was considered to be established in 15 cases (i.e. 44%). In 6 cases (18%) it was considered doubtful and in 13 cases (38%) it remained unknown in spite of the most searching investigation. These figures serve to underline the fact that we are still very far from having solved the problem of the ætiology of polyneuritis.

Extrinsic Poisons

In Gowers' days the commonest causes of polyneuritis were extrinsic poisons of which the most important were alcohol and certain inorganic substances such as lead and arsenic. Nowadays these play a much less prominent role. But the advance of industry and of industrial chemistry has substituted in their place a long list of organic compounds which exert a toxic effect on the peripheral nervous system. To-day a large number of potentially toxic substances are used in flavouring, preserving, or processing foods and as pest destroyers, particularly as insecticides. Six months seldom pass without some new example being reported in the medical press of neuropathies resulting from poisoning by such agents. Poisoning by tri-ortho-cresyl phosphate is perhaps the best-known example of this group, but a series of cases caused by methyl mercury compounds reported by Hunter *et al.* (1940)

was equally dramatic and the same author (Bidstrup and Hunter, 1952) is about to publish some cases caused by a complex fluorophosphate compound. Other cases have resulted from the use of a variety of domestic insecticides. It seems reasonable to suppose that unrecognized examples of this kind account for some of the cases in which the ætiology remains unknown. In watching for them we should bear in mind not only the possibility of chemical agents being toxic to man, but also the fact that individuals in ignorance may employ these agents improperly, or may have an idiosyncrasy, either congenital or acquired, to their action.

Intrinsic Poisons

Of intrinsic, or metabolic poisons as causes of neuropathy, diabetes, the commonest and best-known member of this group remains as mysterious as it was in Gowers' day. He observes that diabetic peripheral neuritis is not related to the amount of sugar in the urine and suggests that it is the result of the perverted metabolism present in the diabetic state. The literature of recent years does not, I think, contain any real advance in our knowledge of its mechanism. This is surely a challenge to anyone looking for a subject for clinical investigation.

A more recently recognized member of this group is the neuropathy associated with acute porphyria. First recognized in connection with poisoning from the sulphonal group of drugs, a considerable number of cases have now been reported in cases of naturally occurring porphyria which depends upon a heredo-familial error of metabolism. Interesting in itself, it is perhaps more important as a possible prototype of other varieties of metabolic disturbance as yet unrecognized. In this connexion one is reminded of the points of close resemblance between acute porphyria and the most acute cases of dermatomyositis.

Another interesting example of neuropathy associated with a perversion of metabolism is that occurring with amyloidosis. It has long been known that the peripheral nervous system may be involved in classical amyloid disease. It is less well recognized that neuropathy may occur prematurely and before the classical manifestations of the disease are present. For several years past I have been watching with melancholy interest a patient whose peripheral nervous system is being progressively destroyed by amyloidosis—proved by biopsy—and there is still no evidence of any of the accepted causes of this condition or, apart from diarrhœa, of any involvement of the viscera.

Deficiency Neuropathies

An increasingly important place has been given of recent years to dietary deficiencies as causes of neuropathy. The prototype of this group is, of course, beri-beri, a condition whose clinical features have been well known since the seventeenth century, but whose precise cause has been established only in the last thirty years. It is now generally accepted as being due to a chronic deficiency in the tissues of thiamine (vitamin B_1). The other principal member of this group, pellagra, is less clearly defined both clinically and ætiologically and in the years between the wars much work was done—in this country notably by Stannus (1947) in an attempt to elucidate the various combinations of cutaneous and neuritic symptoms arising in different communities living on inadequate diets.

The circumstances of the late war provided further opportunity for studying and clarifying this complex subject and although no clinical syndromes were encountered that had not been described before, it was possible to define more clearly the different varieties of neuropathy and myelo-encephalopathy that might result from a deficient diet and to throw more light on the ways in which they were produced. The subject has been well reviewed by Denny-Brown (1947) and by Spillane (1947). It is clear that the nutritional neuropathies cannot be explained simply by the absence of adequate B_1, or even of the whole B complex from the diet. Among the additional facts that have to be taken into account are:

(*a*) The normal dietary habits of the individual. A diet capable of maintaining an Asiatic in good health may lead to a deficiency state in a Western European. It was noticeable in some P.O.W. camps that deficiency symptoms appeared first amongst those accustomed to eating a lot of meat.

(*b*) The deficiency disorders cannot be explained solely in terms of vitamins. Account needs to be taken of the total protein intake and of its quality, as well as of its relationship to the carbohydrate intake. The fat and mineral content of the diet and the presence of trace metals have also to be considered.

(*c*) Deficiency may arise in the presence of an adequate intake through defects of absorption. The parts played in this respect by dysentery, steatorrhœa and fistulæ are beginning to be understood. The importance of the intestinal flora and its modification by various therapeutic agents has also been recognized.

(*d*) The possibility of the presence in the tissue of an anti-enzyme has to be borne in mind. It has recently been shown that a form of neuropathy can be produced in horses by adding 20% or more of bracken to their hay. This has been shown to be due to the absorption of a thermolabile enzyme which destroys thiamine. A comparable situation exists in the so-called "Chastek" paralysis that occurs in foxes fed on raw fish which has also been shown to be due to the absorption of a thermolabile anti-thiamine enzyme present in certain fish and molluscs.

(*e*) It is necessary also to consider the possibility of "antimetabolites" rendering vitamins ineffective. These substances are closely akin to the vitamins in chemical structure but are more stable. They usurp the place of the vitamins in enzyme systems whose action is thereby brought to an end. Examples of such "structural analogues" are pyrithiamine and oxythiamine in respect of thiamine, sulphapyridine in respect of nicotinamide and mepacrine in respect of riboflavine.

Neuropathies Associated with Carcinoma

I turn now to the interesting group of neuropathies associated with the presence of a carcinoma in other parts of the body. The first group of this kind to be described was that of subacute cerebellar degeneration, first reported by Casper in 1929, by Parker and Kernohan in 1933 and by Greenfield in 1934. At first the association of the neuronic degeneration with a visceral carcinoma was thought to be a coincidence, but gradually the existence of a causal relationship between them has been accepted. Further description of this group is inappropriate to this contribution.

The second group was that first described by Denny-Brown in 1948 under the descriptive title of "Primary Sensory Neuropathy with Muscular Changes Associated with Carcinoma". His 2 cases, each of which had a bronchial carcinoma, presented the clinical picture of a purely sensory polyneuritis which was associated pathologically with a primary atrophic process in the nerve cells of the posterior root ganglia without either inflammatory, or vascular reaction. In addition, there was primary degeneration in the striated muscles which Denny-Brown refers to as a polymyositis. He points out the clinical and pathological resemblance of his cases to the neuropathy produced experimentally in pigs by Wintrobe by feeding the animals on a diet lacking in pantothenic acid.

The third group is that of a polyneuritis of the classical mixed type first described by Wyburn-Mason in 1948. This last group may well prove to be relatively common, as I have personally observed 3 cases in the last few years, a larger number has been collected by workers at the London Hospital and many of our colleagues have encountered a number of similar cases. The primary carcinoma is usually in a bronchus and is commonly so small as to give rise to few if any chest symptoms and may even evade the most careful X-ray examination.

The mechanism whereby a remote carcinoma may give rise not to one, but to at least three apparently distinct disorders of the nervous system is still a complete mystery. It is clear that these cases do not depend upon miliary secondaries, or upon diffuse carcinomatosis of the leptomeninges. The histological appearances are those of a selective degeneration. The multiplicity of the syndromes reminds one of the similar diversity of the clinical pictures seen in the mixed nutritional neuropathies met with during the war when polyneuritis, ataxia, with or without retrobulbar neuritis, and spastic paraplegia appeared under apparently identical circumstances.

Conclusion

Of the important group of peripheral neuropathies commonly referred to as acute infective polyneuritis, I will only say that the evidence that they are in fact "infective" is far from convincing and the nature of the hypothetical infecting agent quite unknown.

My review has, I fear, added nothing to our understanding of the peripheral neuropathies, but I hope that it may have demonstrated that we are at present only standing on the threshold of knowledge of this fascinating subject.

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Professor R. H. S. Thompson (Department of Chemical Pathology, Guy's Hospital Medical School, London): *Some Biochemical Features of the Peripheral Neuropathies.*

It is widely recognized that disturbances of carbohydrate oxidation can profoundly upset the functions of the nervous system. In vitamin B_1 deficiency it now seems, mainly as a result of the work of Sir Rudolph Peters and his colleagues (Peters, 1936), that the chief biochemical abnormality within the nerve cells is a failure in the normal oxidative metabolism of the pyruvic acid formed during the breakdown of glucose. As is well known, vitamin B_1 pyrophosphate is a co-enzyme essential for pyruvate oxidation, and in its absence this oxidation cannot take place; pyruvate therefore accumulates in the tissue fluids and in the blood, and the nerve cells are deprived of their normal source of energy.

In experimental vitamin B_1 deficiency the rise in the level of pyruvic acid in the blood has been clearly demonstrated (Thompson and Johnson, 1935), and in beri-beri also Platt and Lu (1939) found increased amounts. Several groups of American workers have shown that even relatively mild degrees of vitamin B_1 deficiency in man can be detected by estimations of the blood pyruvate level after giving a "loading" dose of glucose to the patient, even though in these less severe states the fasting level may not be abnormal (Bueding, Wortis and Stern, 1942; Williams, Mason, Power and Wilder, 1943).

A deficiency of vitamin B_1, however, is not the only way in which pyruvate oxidation in nerve cells can be inhibited. Quite apart from a failure of the co-enzyme, due to thiamine deficiency, the protein component of the enzyme system may be damaged by some blood-borne toxic substance. Arsenic is an example of such an agent which is particularly relevant to a discussion on peripheral neuritis. Trivalent arsenicals react with the protein of the pyruvate oxidase enzyme by combining chemically with essential sulphur groupings, —SH groups, in the molecule, and as a result the enzymic activity of the protein is lost. Although in this case there is no deficiency of the vitamin-containing co-enzyme the end-result is the same—an inactivation of the pyruvate oxidase system leading to raised levels of blood pyruvate, to a block in the continuous supply of energy to the cell and, in some cases, leading also to a peripheral neuritis resembling that associated with vitamin B_1 deficiency.

Arsenicals are not the only substances that can inactivate this enzyme protein. Certain other heavy metals such as mercury or copper, and metalloids such as antimony, together with certain non-metallic organic compounds, are also toxic to this enzyme. As an example of the latter, the ingestion of sanguinarine, an alkaloid, has been shown to block pyruvate oxidation in this way (Sarkar, 1948), and it seems likely that this is largely responsible for the epidemic dropsy that occurs in parts of India, and which was formerly thought to be a type of wet beri-beri.

It is clear, therefore, that although in a case of polyneuritis due to vitamin B_1 deficiency the blood pyruvate level may be abnormally raised after the ingestion of a dose of glucose, raised values might also be found in other cases due not to a thiamine deficiency, but to the presence of some toxic factor such as I have just mentioned. In view of this it seemed of interest to study blood pyruvate levels not only in cases of polyneuritis in whom there was some reason to suspect a thiamine deficiency, but in an unselected series of cases in order to discover whether any evidence could be obtained of impairment of pyruvate metabolism due to one of these other causes. Through the kindness of clinical colleagues both at Guy's and at Queen Square and elsewhere nearly 90 cases of peripheral neuritis have now been examined from this biochemical point of view (Joiner, McArdle and Thompson, 1950).

It was found that when compared with the normal values, a considerable number of the cases of peripheral neuritis showed abnormally high levels of pyruvic acid, 16 out of the first 40 cases being above the normal range. It cannot, however, be concluded from these results that all these cases showing high blood pyruvate levels are necessarily suffering from vitamin B_1 deficiency. In the hope of separating those due to a thiamine deficiency from those due to some other cause large daily doses of the vitamin were given parenterally (100 mg. daily by intramuscular injection) and after fourteen days of such therapy the test was repeated. Although it would be unlikely that any decisive clinical change would be brought about in so short a time, we had reason for thinking that the biochemical lesion, and also the blood pyruvate level, should be restored to normal after fourteen days of treatment with this large parenteral dose. 7 of the 14 cases which were studied in this way showed normal blood pyruvate levels after the fourteen days' treatment, but the remaining 7 cases showed no significant change in the blood levels. In 2 cases intensive thiamine therapy was continued for longer periods and the blood tested again later, but again no change in the pyruvate level was observed.

From the point of view of the changes in carbohydrate metabolism that can be detected by these tests it would seem that peripheral neuropathies fall into three main groups:

(1) A type in which no impairment of pyruvate metabolism can be detected. In this group vitamin B_1 deficiency is presumably not playing any important part in the production of the disease.

(2) A type in which there is some block in the path of pyruvate oxidation; raised blood pyruvate levels are found, but can be rapidly restored to normal values by treatment with vitamin B_1.

In this type it would seem fair to conclude that there is a deficiency of vitamin B_1; the deficiency may not necessarily be dietary in origin, but might be due to a failure in absorption or in the proper utilization of the vitamin.

(3) A type, also showing impaired pyruvate metabolism with raised pyruvate levels in the blood, but in whom prolonged and massive therapy with thiamine produces no effect either clinically or on the blood pyruvate levels.

This last type of case might therefore be associated causally with the presence of some circulating substance which combines with and inactivates the protein of the pyruvate oxidase. If arsenic or some other heavy metal were the toxic agent it would be reasonable to attempt therapy with Dimercaprol.

The chemical method which is in general use for the estimation of pyruvic acid is, unfortunately, not completely specific. It is essentially a method for the estimation of keto-acids which has been

elaborated in such a way as to make it particularly suitable for the determination of pyruvic acid. It will however, to a certain extent, estimate also other closely related keto-acids.

Consequently, it is important in the first instance to identify more exactly any keto-acid which we estimate by this method. It has already been established from experimental work with animals that the keto-acid which accumulates in the blood in thiamine deficiency is pyruvic acid. It has in fact been isolated in the form of a crystalline derivative from the blood of animals deficient in vitamin B_1.

But with polyneuritis of the third type that I have mentioned above, i.e. associated with raised levels of pyruvic acid in the blood which are not restored to normal by treatment with thiamine, we felt that it was necessary to determine whether this excess keto-acid which we are calling pyruvic acid is really pyruvic acid itself, or some closely related keto-acid resulting from some similar but distinct metabolic disturbance.

We are therefore now attempting to identify more precisely the keto-acid accumulating in the blood of patients whose peripheral neuropathy does not appear to be associated with any simple deficiency of thiamine. For this purpose we have used the technique of paper chromatography which was first applied to the separation and identification of the coloured 2:4-dinitrophenylhydrazones of keto-acids by Cavallini, Frontali and Toschi (1949). By this technique it is possible to separate out the different keto-acids present in blood on a strip of filter-paper, and to identify them by comparing their positions with those taken up by the hydrazones of pure keto-acids, under the same conditions.

In blood from healthy subjects only 3 keto-acids are present in detectable amounts—aceto-acetic acid, α-ketoglutaric acid and pyruvic acid, and of these pyruvic acid is present in greatest amount.

Having separated and identified the pyruvic acid by this means it is then possible to cut out the piece of paper carrying the coloured spot, and to extract and estimate quantitatively the amount of pyruvic acid or other keto-acid present.

So far we have only investigated one case of peripheral neuritis by this technique, but in this patient we were able to show that the large increase in keto-acids occurring after the ingestion of glucose was mainly due to pyruvic acid, although some increase in aceto-acetic acid was also present; the level of α-ketoglutaric acid was within the normal range.

We are left with the problem of those cases in which no abnormality of pyruvate metabolism can be demonstrated, and here it would seem that if we are to look for any underlying metabolic abnormality, we must consider the possibility of disturbances of other biochemical systems. A clue to another possible type of causative lesion is provided in the case of the syndrome produced by poisoning by tri-ortho-cresyl phosphate or by certain of the organo-phosphorus compounds that are now coming into use as insecticides.

It has been known for many years that tri-ortho-cresyl phosphate can produce a flaccid paralysis and demyelination of peripheral nerves and of tracts in the cord in man. But the mechanism by which it produces these changes is obscure. Bloch in 1941 first reported that tri-ortho-cresyl phosphate is an inhibitor of cholinesterase, and he suggested that the motor paralysis might be due to inactivation of the cholinesterase at the motor end-plates, in the affected muscles. There are, however, a number of aspects of the problem which would be hard to reconcile with this view, and when we put it to the test we found that the cholinesterase present at the motor end-plates and at synapses is not inhibited by this compound, whereas the so-called "pseudo-cholinesterase" (a closely related enzyme) present in the plasma is highly sensitive to it (Earl and Thompson, 1952). This pseudo-cholinesterase is also present in the peripheral nerves and in the central nervous system, where it appears to be particularly associated with the white fibre tracts. And although the true cholinesterase of the C.N.S., located chiefly in association with the synapses, is insensitive to tri-ortho-cresyl phosphate the pseudo-cholinesterase of nerve tissue is markedly inhibited by relatively low concentrations of this substance.

Further, if animals (chickens) are poisoned by oral administration of a single dose of this compound, and if the brain or spinal cord is examined at intervals after poisoning, it is found that while the level of true cholinesterase is within the normal range, the level of the pseudo-cholinesterase activity is very substantially lowered. The fall in the level of this enzyme in nerve tissue is present and maximal as early as one day after the ingestion of the tri-ortho-cresyl phosphate. The paralysis and demyelination on the other hand do not appear until later.

The inhibition of the pseudo-cholinesterase therefore precedes the onset of histologically detectable demyelination and paralysis, and so cannot be regarded as a result of changes in the myelin sheath induced by some other mechanism.

There is no evidence of any disturbance of pyruvate metabolism in birds poisoned with tri-ortho-cresyl phosphate: the blood pyruvate levels are unchanged and preparations of brain tissue from intoxicated birds which show a profound fall in the level of pseudo-cholinesterase are found to oxidize both glucose and pyruvate at the normal rate. It would seem, therefore, that in the case of the motor polyneuritis induced by poisoning with tri-ortho-cresyl phosphate, a fundamentally different biochemical disturbance exists from that found in vitamin B_1 deficiency or in an arsenical polyneuritis.

Unfortunately, we have at present no clear understanding of the physiological role played by the pseudo-cholinesterase. Its presence in relatively high concentrations in medullated nerves and in the

fibre tracts of the central nervous system suggests that it might have some role to play in connexion with the metabolism and turnover of myelin (Ord and Thompson, 1952), and that when it is inhibited, as by tri-ortho-cresyl phosphate, demyelination and signs of neurone dysfunction may ensue. This possibility would seem to be supported by a recent report of flaccid paralysis developing in 3 people exposed to a new organo-phosphorus insecticide (Bidstrup and Hunter, 1952) which is also a powerful inhibitor of pseudo-cholinesterase; in the brief report of the cases attention was drawn to the fact that the paralysis resembles that which follows poisoning by tri-ortho-cresyl phosphate.

The aspect of these findings that seems to be of significance is that here again we have evidence of an enzymic disturbance accompanying a peripheral nerve lesion, although of a very different type from the block in pyruvate metabolism that occurs in certain other neuropathies.

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Dr. W. B. Matthews: *Cryptogenic Polyneuritis.*

The literature of polyneuritis is largely concerned with the discovery of new causes of the condition or with the description of groups of cases of unknown ætiology that appear to form distinct clinical syndromes. There are comparatively few reports on the relative incidence of the numerous types of polyneuritis that have been described. It therefore seemed worth while to review those cases admitted to the Neurological Unit at the Manchester Royal Infirmary in the eleven-year period 1940–50 inclusive. I am grateful to Dr. F. R. Ferguson and to Dr. G. E. Smyth for permission to report on their patients.

The cases in this survey do not form a representative group of peripheral neuropathies for a variety of reasons. Only in-patients were considered, which excludes many minor manifestations of diabetic neuropathy in particular. The age incidence is probably weighted in favour of the older age groups, although some children are included. Most important is that the series undoubtedly contains a greater proportion of chronic or difficult cases than would be encountered on a general medical unit. Some patients were admitted during this period a considerable time after the onset of their disease so that in these cases the follow-up exceeds the eleven-year period.

When doubtful cases had been excluded 46 patients remained to be considered. The ætiological factors concerned are shown in Table I. The most striking feature is the large proportion in which

Table I.—Ætiological Factors in Cases of Polyneuritis Admitted to the Neurological Unit at the Manchester Royal Infirmary, 1940–50

Carcinoma of breast	1
Carcinoma of bronchus	1
Ethyl alcohol	2
Methyl alcohol	1
Porphyria	1
Diabetes	2
Hyperemesis gravidarum	1
Diphtheria	1
Infective hepatitis	1
Measles	2
Mumps	1
Unknown	32
Total	46

Table II.—Influence of Age on Prognosis

Average age of patients at onset of attack:

Good prognosis	30·2 (range 5–48)
Bad prognosis	43·2 (range 21–61)

Age at onset	Good prognosis	Bad prognosis
Under 30	7	2
30–40	5	3
40–50	5	6
50 and over	0	4

no convincing cause could be found—some 70% in fact. Moreover, in many cases classified as of known ætiology the agent incriminated is more a well-recognized clinical association than a clearly understood causal agent. For example, an acute polyneuritis occurring three weeks after measles is classified as of known ætiology, while a similar attack following a non-specific infection is classed as of unknown ætiology.

It is with the 32 cases of cryptogenic polyneuritis that I shall deal. Recognized causative agents may have been overlooked in some instances, though many investigations were carried out. In chronic cases these were as thorough as knowledge of the pathogenesis of polyneuritis at that time permitted. While recognizing therefore that different unknown ætiological factors and mechanisms might be involved, it was hoped that a clinical study of these patients might throw some light on two important aspects. It was thought that on viewing the cases in retrospect it might be possible (1) to discover prognostic indications by which the course of the disease might have been predicted. Closely linked with this was (2) the possibility of distinguishing clinical syndromes that might later perhaps be found to be associated with specific causes or metabolic defects. I must say at the outset that the results were somewhat inconclusive.

(1) *Prognostic Indications*

The results of the follow-up of 31 of these 32 patients were that the prognosis was good in 15 patients and bad in 16, 7 patients having died of the disease. (One patient was lost sight of). Post-mortem examination in 5 of these still failed to show any cause for the condition. Although the term "bad prognosis" includes a variety of end-results I think that the distinction between complete recovery and permanent, progressive or fatal lesions is sufficiently clear-cut to warrant such a broad subdivision.

The prognosis was rather better in women but the difference was not significant. Age appeared to be an important prognostic factor. It can be seen from Table II that the mean age at the onset of the disease in those who recovered was 30·2 years, and in those who did not, 43·2, the difference being statistically significant. Amplifying this it can be seen that the prognosis becomes increasingly menacing with advancing age so that of those in whom the disease began after the age of 50 none recovered. In 2 cases of recurrent polyneuritis it was possible to include separate attacks. One patient recovered from attacks when aged 41 and 45 and the other recovered from severe attacks when 21 and 45 but died of his third attack at the age of 59. 2 patients had to be omitted owing to uncertainty of the significance of certain possibly premonitory symptoms.

The occurrence of a preceding non-specific infection or of fever during the attack was rare and neither appeared to have any bearing on the prognosis. The electrocardiogram was abnormal in only 2 of the 10 patients in whom it was examined. One otherwise healthy young man had a bundle branch block which was still present two years after his recovery and which may have been unrelated to his polyneuritis. The other patient, who showed non-specific changes in the chest leads, died after a progressive course of five months. Significant tachycardia was uncommon and usually either settled quickly on admission to hospital or was a terminal event.

The cerebrospinal fluid protein was found to have both normal and greatly raised values not only in patients who recovered quickly but also in fatal or extremely chronic cases. There seemed to be no foundation for the belief that a high protein indicates a good prognosis.

The extent of the paralysis was again found to be unhelpful beyond the obvious fact that bulbar involvement is an immediate danger to life. Patients with severe quadriplegia recovered, while one patient in whom paralysis was never marked outside the legs died from the resulting bedsores. In 2 patients who died the paralysis was markedly asymmetrical at the onset. It is also perhaps worth mentioning that in 2 patients in whom the disease subsequently followed an extremely chronic course there had been previous episodes of facial palsy. In one this may have been coincidental, but the other had no less than three such attacks, two on one side and one on the other.

The degree of sensory loss was also found to be no guide to the ultimate prognosis. A clinically pure sensory neuropathy was not, however, encountered as a recoverable lesion, but was seen twice as a permanent residue of an acute attack of motor and sensory neuropathy and once as a steadily progressive condition.

All patients received treatment similar in outline—physiotherapy and large doses of vitamin B_1. It could not therefore be said that treatment had any effect on the prognosis.

As might be expected the mode of onset was found to be of considerable value in prognosis. Following Magnussen (1946) the clinical course of the disease was divided into three stages: progressive, stationary and improving. Those in whom the progressive stage lasted less than eight weeks were classified as of acute onset, although it is obvious that the term, as defined, may imply something very different from the acute onset of poliomyelitis, for example. Table III shows that such a subdivision confirms the generally held opinion that cases with an acute onset have on the whole a better prognosis, but it is important to note that the distinction is far from absolute.

Onset of improvement.—This could always be dated with some accuracy. It can be seen from Table IV that there is a fairly sharp dividing line at three months. If there had been no improvement within this period recovery was much less likely to occur. Again there are exceptions, both those who began to improve within this period but who never recovered completely, and those whose disease was progressive or stationary for a longer period, but who subsequently recovered.

TABLE III

	Recovered	Died	Residual or progressive lesions
Acute onset ..	12	2	4
Slow onset	4*	5	5

*Includes two attacks in one patient.

TABLE IV

Time from onset to death or to the first sign of improvement	Recovered	Died	Residual or progressive lesions
Less than 15 days ..	2	2	1
„ „ 70 „ ..	8	2	4
„ „ 90 „ ..	12	2	4
More than 90 days or no improvement	4*	5	5

*Includes two attacks in one patient.

It cannot be said that reviewing these 31 cases in retrospect has brought to light any absolute prognostic indications. Any such attempt is overshadowed by the existence of recurrent polyneuritis. The only possibly significant fact with regard to this problem is that both the patients with recurrent attacks remarked that during the long intervals of good health between attacks they remained liable to short episodes of paræsthesiæ when over-tired, a symptom not complained of by patients who recover from a single attack of polyneuritis.

(2) *Different Clinical Entities*

On turning to the second object of this survey, the attempt to distinguish clinical entities, the difficulties are again great. These cases might be classified in a variety of ways according to the mode of onset, clinical features or end-result, but any such categories always showed a considerable degree of overlap. For such cases there are three descriptive titles in common use—acute infective polyneuritis, chronic progressive polyneuritis and recurrent polyneuritis. The first of these has received most attention, and comparatively minor clinical variants of a common picture have often been given distinctive names and rather rigid diagnostic criteria. The clinical features of the other classes are ill-defined. In the present series there are 18 cases that might reasonably be thought to come under the heading of acute infective polyneuritis, although the infective element was seldom evident. Of these 12 recovered, 2 died in the acute stage and 4 were left with residual lesions. 1 patient was left with a bilateral facial palsy; 1 with foot-drop and wasted hands; and 2 with incapacitating sensory ataxia which remained stationary for many years. In both these latter cases the initial severe paralysis had recovered, but 1 patient, five years after the initial acute attack, is now again becoming weak and wasted, but this time the onset has been gradual.

10 cases may be regarded as chronic progressive polyneuritis. The clinical course in these cases was extremely variable and the duration and outcome can only be summarized in Table V. There is an

TABLE V

Case No.	Clinical course
1	Death after five months
2	Progression for eight months. Recovery after two years
3	Death after twelve months
4	Progression for twelve months, then stationary for two years
5	Death after nineteen months
6	Progression for four years. Recovery after six years
7	Death after four years
8	Progression for fourteen years
9	Progression for sixteen years
10	Progression for twenty-four years

obvious clinical distinction between the disease steadily progressive over decades and the acute attack spending its force within a few weeks. It can be seen, however, that apart from the last 3, these cases form a fairly continuous series, and the distinction between the more acute of these chronic progressive cases and those classified as of acute onset becomes less obvious. Except in progressing for longer than an arbitrarily defined limit such cases may be indistinguishable. It must be doubted whether the descriptive titles of acute infective and chronic progressive polyneuritis do in fact describe distinct entities.

Of the remainder 2 are classified as recurrent polyneuritis with recovery between attacks, and one patient was altogether remarkable and could not be placed in any of the recognized categories.

In conclusion it may be said that this review has emphasized the limitations of the purely clinical approach to polyneuritis. Polyneuritis is a response of the nervous system to a great variety of stresses, many as yet unknown. By reason of this lack of specificity the study of variations of clinical detail within this pattern does not appear likely to throw much further light on cases of unknown origin or on the fundamental pathogenesis of polyneuritis.

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[*May* 1, 1952]

Some Observations on the Structure of Myelin
[*Abstract*]

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THE submicroscopic structure of myelin has been studied by a combination of X-ray diffraction and micro-analytical techniques. Low angle X-ray diffraction patterns furnish an indication of the crystalline structure of myelin [1, 2]; the aim of the present studies was to determine the role played by water, and by various lipids in the architecture of the myelin unit. Frog sciatic nerve was used in initial experiments, though, more recently, the studies have been extended to bovine optic nerve [3]. The source of X-rays was a high-power rotating-anode unit, making possible relatively short exposures (of some ten to fifteen minutes' duration). Special observation cells provided a means of exposing a short (8 to 10 mm.) segment of nerve to a varying environment, while at the same time interfering as little as possible with the rest of the preparation. X-ray diffraction patterns were recorded serially in the affected segment, and nerve conductivity tested throughout most experiments where fresh nerve was used. The effects of graded water loss, variations in temperature (from −20° C. to 200° C.), and of swelling and slow extraction by lipid solvents and their vapours (e.g. ethyl alcohol, acetone, ether, chloroform) have been studied. The results have been compared with those obtained in similar experiments using pure synthetic phosphatides, "strandin" [4], lipid mixtures and wet and dry total lipid extract of nerve.

The changes observed in nerve during slow drying followed a definite sequence [2] which showed a reversible and an irreversible phase. The effects of freezing resembled those of drying. Changes in diffraction pattern appeared particularly marked between 58° C. and 61° C. [5]. Ethyl alcohol, acetone and ether all readily affected spacings below 70° Å in the dried nerve pattern. Spacings above 70° Å were much more susceptible to alcohol than to either acetone, ether or chloroform [6]. The results suggest the existence in myelin of a highly ordered, laminated, lipid-lipoprotein unit. The hydrocarbon chains in some layers of the unit may be tilted with respect to the radial axis, and unesterified cholesterol may play an important role in maintaining stability between adjacent chains. The effects of the various procedures on the X-ray diffraction pattern could, in part, be accounted for by an alteration in balance between polar and non-polar cohesive forces, penetration of micelles by lipid solvents, and the polymorphism of lipids over a temperature range.

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Section of Comparative Medicine

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[*May* 21, 1952]

Neoplasms in Cats

By E. COTCHIN, M.R.C.V.S.

IN his book on the Natural History of Cancer, published in 1908, W. Roger Williams writes: "It appears to me that the chief feature in which animal tumours differ from their human congeners is in respect to the relative frequency of site incidence; and this, I suspect, is mainly the outcome of the diversity of function and structure of certain organs, which, in their turn, ultimately depend upon differences in habit and mode of life." The truth of the first part of this statement can again be illustrated by considering the tumours we have found to occur in cats and by comparing the incidence of the different tumours with that seen in other domestic animals and in man, paying particular attention to the situation in the dog, the animal whose tumours have been most studied. My remarks are based on a survey, recently published (Cotchin, 1951), of the 1,211 tumours from dogs and 115 tumours from cats examined in the Department of Pathology at the Royal Veterinary College in London in the decade ending December 1949, and a further 111 tumours from cats that I have examined there since then. For reasons given elsewhere, the result of the survey of the first group of 115 neoplasms was a provisional one only, and the second group of 111 tumours is still under study, so that the data given are subject to alteration, but it is likely that any changes would affect only the histological classifications, and the figures given as to site incidence are likely to be exact. This total of 226 tumours is very small but from them and from the literature (*see*, for example, Lombard, 1940; Verardini, 1935), a tentative picture can be formed of the common neoplasms of the domestic cat. Most of our material is from London cats, and the findings might well not apply to cats in other parts of this country, or in other countries.

A number of surveys of post-mortem and clinical material have been published, which give an idea, which must be only a very approximate one, of the incidence of neoplasms in the different species of domestic animals. It is generally agreed that the order of frequency with which tumours occur is probably: dog—common; horse and ox—much less common; sheep and pig—rare, with the cat falling somewhere behind the dog. This order is, of course, not that of the different animal populations in this country (sheep, cattle, dog, pig, horse—the size of the cat population is not known but one estimate has put it at 9 millions, which would place the cat after the sheep in this list). There are for animals no figures available for cancer as a cause of death as in the Registrar-General's Report which indicates that in this country the order of system incidence of carcinoma registered as a cause of death in humans is: alimentary, female genital, respiratory, and male genital, chiefly. The outstanding difference here from animals is the higher proportion of respiratory cancer in man. There are also species differences in the frequencies with which different organs in the various systems are affected.

Reports in the literature, and the experience of Knight and Douglas (1943) at the Royal Veterinary College, suggest that the incidence of neoplasms in the dog is of the order of 5% of animals examined in the clinic, and in the cat is of the order of 1%. Some experienced clinicians have suggested to me that tumours in cats, which are generally thought to be uncommon, are being encountered with increasing frequency. In the ten-year series referred to above the order of incidence of 1,211 tumours from the dog was: skin and associated structures 42%, female genital system 22·2%, alimentary system 16·8%, male genital 6·9%, skeletal 3·4%, endocrine 1·4%, hæmopoietic (leukosis) 1·1%, and urinary 1·0%. This may be compared with the incidence of the total of 226 cat tumours now being dealt with.

SYSTEM INCIDENCE OF 226 NEOPLASMS IN CATS

Skin	68	Urinary	6
Alimentary	66	Endocrine	6
Female genital	22	Respiratory	4
Skeletal	20	Miscellaneous	14
Lymphatic	20		
		Total	226

Thus, about 30% of the tumours were from the skin, 30% from the alimentary system, and 10% from each of the female genital, skeletal and lymphatic systems. Noteworthy is the absence of specimens from the male genital and central nervous systems, and there are few reports in the literature of tumours from these sites—they include a carcinoma of the penis (*see* Lombard, 1940), a glioma of the cervical cord (Milks and Olafson, 1936), and a tumour (? ependymal) of the choroid plexus of the fourth ventricle (Steensland, 1906). It is possible that few tumours occur in the male genital system due to the fact that so many male kittens are castrated, and the C.N.S. is not often thoroughly examined post mortem. The high incidence of skin and alimentary tumours may, of course, be due to the fact that tumours in these systems either can be seen easily by the cat's owner, or interfere with a major bodily function, but it might be significant that these systems are also those that would be the first to come into contact with carcinogenic agents that might be present in the environment or food.

Age incidence.—Tumours occur at all ages in cats, but with increasing frequency with advancing age. Of the 184 cats in this series whose age was known, 68·5% were between 6 and 12 years old.

Age (years)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
No. of tumours	6	3	5	6	8	13	11	15	29	19	23	16	6	6	5	4	7	2

Sex incidence.—Of the 172 cats whose sex was recorded, 127 were male (101 castrated), and 45 female (16 castrated).

The tumours of the various systems may be briefly reviewed:

(i) *Skin.*—As compared with the dog, a narrower range of types of skin tumours has been encountered in the cat. The circumanal adenoma of the dog does not, and indeed cannot, occur in the cat. Of the 68 skin tumours examined, 40 were of epithelial type, and of these 31 were of basal-cell or glandular type. In the cat, as in the dog, typical keratinizing epidermoid carcinoma is uncommon. In the dog, skin gland tumours are found predominantly in males, and at least 28 of these 40 epithelial tumours in cats were known to occur in males (21 castrated), while only 2 were known to occur in females (2 castrated). At least 8 of the basal-cell types were pigmented.

Of interest is the occurrence of tumours of the ceruminous glands, of which 5, and probably 8, examples were found, at least 4 being malignant. These ceruminomas, very rarely described in man (Gates, Warren and Warvi, 1943), have been described before in cats (for example, by Ball, Collet and Girard, 1938). The tumour may be first noticed as a skin ulcer or swelling below the ear.

(ii) *Alimentary system.*—In man, a great proportion of alimentary carcinomas are found in the stomach or large intestine, but these, and particularly the stomach, are rare sites of carcinoma in the cat, or indeed in any domestic animal. In the dog, we found the following site incidence for 204 alimentary tumours: Mouth (including 50 tonsil) 134; intestines, mesenteric node 40; liver 21; pancreas 4; stomach (no carcinomas) 3; salivary gland 1; œsophagus 1. In the dog, carcinoma of the œsophagus or of the tongue is almost unknown, but in the cat, alone of the domestic species, carcinoma of these organs, as in man, appears to be not uncommon. Thus, 36 of the 66 tumours in the alimentary system of cats were carcinomas, distributed as follows: œsophagus 13, tongue 7, tonsil 5, small intestine 4, pharynx 3, pancreas 3, liver 1.

(*a*) *Tongue:* 7 carcinomas were seen. The predominant site appears to be the left ventrolateral surface of the tongue at about the level of the frænum. While the tumour may not appear very large externally, deep invasion of the tongue musculature may occur. Metastasis to the local lymph node may also occur. The average age of affected animals was 10½ (5–16) years. All the animals affected were males, 5 of the 7 being castrated.

(*b*) *Tonsil:* Probably the commonest single malignant tumour of the male dog, carcinoma of the tonsil, also occurs in cats, 5 examples being seen. The average age of the cats was 9½ (6½–13) years, and at least 4 of the affected animals were castrated males. As in the dog, the primary tumour may remain inconspicuous while the secondary deposit in the local node, which probably always develops, may be very large.

(*c*) *Œsophagus:* Carcinoma of the œsophagus is in our experience one of the commonest malignant tumours of cats. The average age of the affected animals was 11½ (9–18) years. At least 9 of the 13 animals were males (7 being castrated), and only 2 (both entire) were known to be females. The common site of the tumour was at the level of the entrance to the chest. Local invasion of the wall of the trachea may occur.

(*d*) *Intestine:* The majority of the tumours of the bowel were sarcomas (chiefly lymphosarcomas), 10 examples being seen (average age of cats 9¾ (7–13) years), but 4 cases of carcinoma of the small intestine, of which 2 involved the duodenum, were seen.

More alimentary tumours in humans occur in males than in females, but the higher incidence in castrated males in this series of cat tumours might suggest that this may be related rather to the absence of female, than the presence of male, endocrine factors.

(iii) *Female genital system.*—Tumours of this system, in the dog and cat, occur most often in the mammary gland, but in our series of tumours from cats others were also seen—an ovarian adenocarcinoma, a lymphosarcoma and two leiomyomas of the uterus, and three fibromas of the vagina. One striking contrast with the dog, as regards mammary tumours, is that in the cat the majority of the tumours are malignant, 13 of our series of 15 being carcinomas. The average age of affected animals was 11½ (9–16) years (*see also* Nielsen, 1952).

(iv) *Skeletal system.*—As in the dog, the tumours of bone that were seen were malignant, and the limb bones were the common site. Of the 20 bone sarcomas, at least 9 were from the humerus and 5 of the others were in the femur.

(v) *Lymphatic system.*—The 20 cases comprised 6 examples of lymphatic leukosis and 14 sarcomas of the mesenteric lymph nodes, of which 6 or 7 appeared to be angiosarcomas. The average age of cats showing these mesenteric node sarcomas was 9·8 (6–12½) years, and males predominated (7/9). Metastases were often seen in the liver.

(vi) *Urinary system.*—2 of the 6 renal tumours were embryonal nephromas, and 4 were lymphosarcomas. The latter occurred as single, diffuse or multiple lesions in the cortex, with diffuse interstitial lymphocyte accumulation. These so-called "sarcoma kidneys" of the cat may, however, actually represent metastatic foci of lymphosarcomas originating elsewhere.

In the 6 endocrine system tumours are included 4 lymphosarcomas of the thymus and a thymoma (these should perhaps be grouped in the lymphatic system) and a possible chromophobe-cell adenoma of the pituitary. While lung carcinomas have been reported in the cat (Lombard, 1940), only one possible primary carcinoma of the lung was seen in this series. Three tumours of the nasal cavities were encountered (two sarcomas and a carcinoma); neoplasms in this site are to be distinguished from tuberculous lesions.

Summarizing, we have found the following tumours most commonly in the cat: Glandular and basal-cell tumours of the skin; carcinoma of the œsophagus and tongue; carcinoma of the mammary gland; osteosarcoma of the humerus; lymphosarcoma of the intestine; sarcoma of the mesenteric lymph nodes.

In conclusion, a further quotation may be given from W. Roger Williams's book (1908): "Although progress has lately been made, the comparative pathology of tumours is still in a rudimentary and backward condition." Despite the well-known work of some medical and veterinary pathologists in this field, e.g. Willis, Jackson, Feldman, Innes, Mulligan in the English-speaking world, this still remains largely true. There are a number of reasons why so few intensive studies of the tumours of domestic animals have been made—the main reason probably being that it is desirable that research work should be directed to diseases that are of economic importance. However, neoplasms in domestic animals are worth studying, for the following reasons:

(1) To provide a satisfactory basis for diagnosis and prognosis in veterinary practice.

(2) These neoplasms may be found to be of importance as indicators of possible ætiological factors, extrinsic or intrinsic. Practically nothing is known about possible variations in incidence of neoplasms of domestic animals in different countries and studies in this direction might usefully supplement those being made in man at the present time.

(3) The domestic animals bridge the gap of size between man and the smaller experimental animals, and spontaneous tumours in them could be used for experimental therapeutic studies. A special organization might be needed for this work.

(4) The occurrence or non-occurrence of certain neoplasms, as seen in man, in the domestic species might be a useful check on hypotheses as to the causes and nature of cancer in man. To be of any value in this respect, the number of animals examined would need to be greatly increased.

Further progress in the study of neoplasms in domestic animals might be aided by:

(1) An agreed nomenclature (this problem, along with the problem of nomenclature of animal diseases in general, is being tackled by a committee of the International Veterinary Congress).

(2) A registry of animal tumours.

(3) A critical survey of the literature.

(4) Experimental studies.

Much work could be done on animal tumours, but what sort of studies would be worth making will need careful consideration, so as to conserve the resources available for the best possible ends.

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Anticomplementary Substances in Experimental Infections

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THIS work is described *in extenso* in *Brit. J. exp. Path.* (1952) **33**, 327.

The Effect of Added Vaccines on Diphtheria Antitoxin Production

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NEARLY fifty years ago Michaelis (1904) stated that the simultaneous injection of two antigens might adversely affect the degree of immunity produced by either or both. That there is, however, no such "competitive action" of antigens is apparent from much laboratory and clinical evidence since made available: indeed this evidence indicates that the degree of immunity acquired from the action of one antigen may in fact be increased by the presence of another.

The work of Glenny and his associates (1926) has clearly demonstrated the superiority of toxoids adsorbed on mineral carriers over plain fluid toxoids as antigens. It was Holt and Bousfield (1949, 1950) who demonstrated the importance of the amount of mineral carrier as a factor determining the degree of acquired immunity, and the adsorbed toxoid is to-day the product of choice for use as a single antigen.

In combined prophylactics, however, the presence of organized particles (bacterial cells) is another factor that may have the same effect on the antigenic response as has a mineral carrier. In laboratory experiments I have shown (Ungar, 1952) that in the combined pertussis-diphtheria prophylactic the aluminium phosphate can be reduced in amount or even omitted altogether without significantly affecting the antitoxin response of immunized guinea-pigs. The few reports on the correlation between intramuscular injections of aluminium salt containing antigens and paralysis of the injected limb in poliomyelitis cases have induced further experiments to compare the antigenic responses to plain suspensions of *H. pertussis* and fluid toxoids compared with those due to the same antigens adsorbed on aluminium phosphate.

We have found the omission of the mineral carrier to have no effect on the degree of immunity produced against pertussis in mice or rabbits immunized with the two types of vaccines. The present communication gives the results of experiments on guinea-pigs and mice into the effects of various factors on the level of diphtheria antitoxin.

From Tables I and II it may be seen that decreasing the amounts of aluminium phosphate in the combined vaccine from 8·75 to 2·5 mg./ml. has no effect on the final value of the antitoxin.

TABLE I.—DIPHTHERIA ANTITOXIN RESPONSES OBTAINED IN GUINEA-PIGS IMMUNIZED WITH DIPHTHERIA/PERTUSSIS PROPHYLACTIC

Groups of guinea-pigs were immunized with 1 Lf injected subcutaneously on two occasions (T.S.A. Regulations)

Batch No.	Final $AlPO_4$ mg./ml.	Final pertussis conc. × 10^6 orgs./ml.	No. guinea-pigs immunized	Diphtheria antitoxin response units/ml. geometric mean
1	2·5	20,000	10	2·34
2	5·0	,,	,,	2·00
4	8·75	,,	,,	2·12
P.D.	10·0	Nil	,,	1·91
10	2·5	,,	,,	1·85
11	5·0	,,	,,	2·99
12	10·0	,,	,,	3·45
16	Nil	,,	,,	<1·00
17	,,	20,000	,,	2·87
18	3·35	,, A.P.W.C.	,,	3·00
P.D.	6·6	,, A.P.W.C.	,,	2·41

TABLE II.—DIPHTHERIA ANTITOXIN RESPONSES OBTAINED IN GUINEA-PIGS IMMUNIZED WITH DIPHTHERIA/PERTUSSIS PROPHYLACTIC

Groups of guinea-pigs were immunized with 1 Lf injected subcutaneously on two occasions (T.S.A. Regulations)

Batch No.	Final $AlPO_4$ mg./ml.	Final pertussis conc. × 10^6 orgs./ml.	No. guinea-pigs immunized	Diphtheria antitoxin response units/ml. geometric mean
Toxoid 120/122 ..	Nil	Nil	10	<1·00
,, ..	,,	20,000	,,	2·68
,, ..	,,	20,000	,,	3·04

It may also be seen that the amount of aluminium phosphate added to the diphtheria toxoid, when this is used as the only antigen, is a decisive factor in improving the antitoxin response. The omission of the aluminium phosphate from a combined prophylactic is not, however, followed by a drop in the antitoxin level in the blood of immunized guinea-pigs. This observation was made repeatedly and with different batches of fluid toxoids and bacterial suspensions. The enhancing effect of the vaccines on the diphtheria toxoid is not limited to *H. pertussis*; the same phenomenon can be reproduced when suspensions of other bacteria, yeast or even collodion particles are used (Table III). In this connexion it should be noted that mice (but not rats) can be used for the assay of diphtheria antitoxin. As mice are used to a large extent for the assay of pertussis vaccines, the same animal may be used for the evaluation

TABLE III.—DIPHTHERIA ANTITOXIN RESPONSES OBTAINED IN GUINEA-PIGS IMMUNIZED WITH DIPHTHERIA PROPHYLACTIC PLUS DIFFERENT SUSPENSIONS OF ORGANISMS AND COLLODION PARTICLES

Groups of guinea-pigs were immunized with 1 Lf injected subcutaneously on two occasions (T.S.A. Regulations)

Batch No.	Final $AlPO_4$ conc. mg./ml.	Final pertussis conc. × 10^6 orgs./ml.	Diphtheria antitoxin response units/ml. geometric mean
Ref. 19/6/50	Nil	Nil	<0·75
,, ...	5	,,	1·38
Batch 44	10	,,	2·26
,, ...	5	Suspension 20,000	6·07
,, ...	6·6	A.P.W.C. ,,	6·63
,, ...	5	*B. coli* ,,	2·16
,, ...	,,	*Prodigiosus* ,,	3·46
,, ...	,,	Small collodion particles 20,000	2·20
,, ...	,,	Large ,, ,, ,,	2·17
,, ...	,,	Suspension yeast cells ,,	8·50

of diphtheria toxoids in combined antigens—if further work confirms our observation. Like guinea-pigs, mice will produce antitoxin well over 2 units/ml. of blood, if a suitable amount of the toxoid is injected, divided into two doses spaced over a period of four weeks (Table IV).

TABLE IV.—DIPHTHERIA ANTITOXIN RESPONSES OBTAINED IN GUINEA-PIGS AND MICE IMMUNIZED WITH DIPHTHERIA PROPHYLACTIC

Groups of guinea-pigs were immunized with 1 Lf injected subcutaneously on two occasions (T.S.A. Regulations)

Groups of mice were immunized with 1 Lf injected intraperitoneally on two occasions separated by an interval of four weeks.

Batch No.	Final $AlPO_4$ mg./ml.	No. animals immunized		Diphtheria antitoxin response units/ml. Geometric mean	
		Guinea-pigs	Mice	Guinea-pigs	Mice
46A	10	10	20	3·56	4·21
49	,,	,,	,,	2·38	2·65
50	,,	,,	,,	2·44	2·27
P.D.	,,	,,	,,	2·07	3·68

The reason for the enhanced action of the bacterial suspension added to the diphtheria toxoid is open to question. It is not the adsorptive action of the toxoid on the bacterial cell that is responsible as may be seen from Table V. There is hardly any adsorption even at double

TABLE V.—ADSORPTION OF TOXOID ON ALUMINIUM PHOSPHATE

Batch No.	Lf/ml. added	Pertussis/ml. $\times 10^6$ added	$AlPO_4$ mg./ml.	Lf/ml. in supernatants	%Lf units adsorbed
1	28·5	20,000	Nil	27	5·3
2	28·5	40,000	,,	28	1·75
3	57	20,000	,,	55	3·6
4	57	40,000	,,	57	0
5	28·5	20,000	0·5	12	58·0
6	28·5	20,000	1·0	4	86·0
7	28·5	20,000	2·5	0	100·0
8	5·0	Nil	2·5	0	100·0

the bacterial concentration, whereas the antitoxin is completely adsorbed on 2·5 mg. of aluminium phosphate. It is more likely that bacterial cells add to the bulk of the foreign material in the depot formed at the site of injection of the combined prophylactic and thus have a strong local irritant action, as can be inferred from the accounts of the local reactions seen in children after injection of the combined antigen.

The report of Greenberg and Fleming (1947) has a considerable bearing on this problem, for they showed that graded doses of a plain pertussis suspension proportionately increase the immunizing effect of a constant amount of the fluid toxoid.

SUMMARY

Our experiments indicate that the amount of aluminium phosphate can be reduced in the combined diphtheria-pertussis prophylactic, or a carrier may be completely omitted without significantly affecting antitoxin production. As a single antigen the fluid toxoid requires an optimum amount of aluminium phosphate (Holt and Bousfield, 1947) to give a satisfactory antitoxin titre. This observation may well be important in the choice of a combined prophylactic for the immunization of children throughout the year.

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ERRATUM

Section of Comparative Medicine, meeting on March 19, 1952, *Proceedings*, Vol. **45**, p. 480, July 1952:
Mr. P. Stuart: *Bovine Mastitis Resembling Tuberculosis Caused by Rapidly Growing Acid-fast Bacteria:* line 15: The lesions in the nodes were granulomata . . . *should read* The lesions in the udders were granuloma . . .

Section of Experimental Medicine and Therapeutics

President—Professor R. A. McCance, M.D., Ph.D., F.R.C.P., F.R.S.

[*May* 13, 1952]

SYMPOSIUM ON CERTAIN AGENTS USED IN MILLING AND BAKING

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Methods of Bread Improvement

The baking of consistently good bread demands much more technical knowledge and skill than is generally appreciated, the intricacies involved being numerous.

The principal raw material in British bread is wheaten flour, the protein of which possesses the property of forming with water an elastic substance known as gluten, whereas other cereal flours when mixed with water form only a plastic mass. Thus in bread-making when we mix wheaten flour with the correct amount of water an elastic dough is produced. The amount of water required to do this depends on the nature of the flour.

The properties possessed by the elastic dough have a profound effect on the quality of the bread finally produced by its fermentation. Fermentation involves an expansion of the dough resulting from the gas produced within it by the action of yeast on the sugars initially present in the flour and those produced by diastatic action as fermentation proceeds.

During this process a considerable amount of action is caused by the carbon dioxide evolved and the gluten must be adequately elastic and extensible to withstand the expansion it undergoes. Furthermore after fermentation is complete the gluten must remain sufficiently strong to withstand the dividing of the dough into pieces of appropriate weight and their moulding into the final shape required. Whether these operations are done by hand or by machinery the same general principle applies.

After this manual or mechanical treatment which, depending on how it is done, can itself have an effect on the appearance of the crumb of the cut loaf, the dough pieces are given time to recover or prove. They are then baked during which time the dough rises further owing to increased gas production and enzyme activity until the dough temperature is sufficiently high to cause their inactivation, the starch is gelatinized and the gluten coagulates. Thus, it will be appreciated that the final volume, build, crumb characteristics and general appearance of the bread obtained are determined by a variety of factors; nevertheless the physical properties of the elastic protein complex, i.e. the gluten, play a large part in this determination.

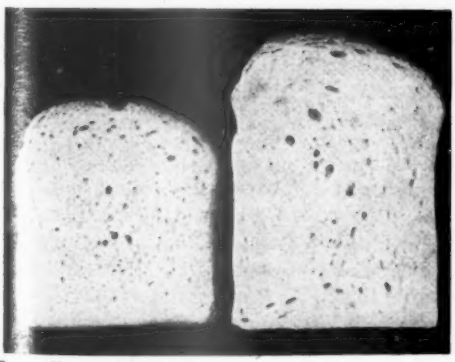

FIG. 1.—The loaf on the left was prepared from freshly milled untreated flour. The loaf on the right is of the same weight, width and length and was prepared from the same flour except this flour had received treatment with a typical improver bleacher. The increase in height and therefore in volume, together with the improved crumb characteristics, are clearly discernible. (Reproduced from Amos, A. J. (1951) *Chemistry and Industry*, p. 947. By permission.)

The physical properties of gluten depend on a number of factors, including the type of wheat from which the flour has been milled. Thus flour milled from a good Canadian wheat gives a strong resilient dough whereas flour from an English wheat would give a weak dough unsuitable for bread-baking, inasmuch as the loaf it would yield would be dense, small in volume and unpleasing to masticate.

A further factor affecting the physical properties of flour protein, and therefore the behaviour of the flour on baking, is storage. In some flours even a few weeks' storage causes a noticeable improvement in baking quality due to increased strength, stability and elasticity in the dough. It was because the bread produced from freshly milled flour was not of such good quality as bread prepared from "aged" flour that it became common practice in the milling industry not to despatch flour to the baker for some weeks after milling. Nevertheless ageing by storage does not occur at a uniform rate for all flours and this can easily be demonstrated by comparing the increase in bread volume brought about by a specified period of ageing in flours milled from different wheats.

Thus both practical and economic factors associated with natural ageing on a large scale point to methods being required for increasing the speed of ageing flour and producing a more uniform material with its bread-baking qualities well developed, if consistent and good bread is to be baked from it.

It is now nearly forty years since it was found that the incorporation in the flour of a very small amount of ammonium persulphate (decomposing to ammonium sulphate on baking) promptly brought about the same effect as natural ageing. This substance was therefore the first chemical flour improver. Since then the advent of dough-testing instruments and more exact test-baking techniques have made it possible for the miller to adjust the quantities of flour improvers used according to the requirements of the flour protein which depend on the various wheats constituting the grist.

Table I gives a list of some of the materials used in flour treatment. It will be noticed that certain substances have a bleaching effect on flour in addition to an improving action. The bleachers used by the miller have one function only and that is to remove the natural yellowness of flour due to the presence of coloured xanthophylls and other pigments. Bran pigments are not affected by bleachers and it is for this reason that 85% and 81% extraction flours do not appear so bright as flour of lower extraction rates, nor do the breads prepared from the former appear so white.

TABLE I.—FLOUR TREATMENT—SOME EXAMPLES

The quantities used depend to some extent on the extraction rate of the flour treated in addition to the quality of the individual flours. Generally the quantities would be slightly less for whiter flours and greater for flours of high extraction rate.

The figures given are the approximate effective amounts based on flour weight for untreated 81% extraction flour.

Treatment	Other name	Effect	Amount of the pure substance expressed as a % and parts per million
Nitrogen trichloride ..	Agene	Bleaches and improves	0·006 (60)
Chlorine dioxide ..	Dyox	Bleaches and improves	0·003 (30)
*Benzoyl peroxide ..	Novadelox	Bleaches	0·0015 (15)
*Potassium bromate ..	Various proprietary names	Improves	0·0020 (20)
Ascorbic acid	Vitamin C	Improves	0·0020 (20)
*Ammonium persulphate	Salox	Improves	0·016 (160)

*The commercial products in powder form are diluted with inert materials to facilitate handling.

All these flour improvers except ascorbic acid are oxidizing agents; it is known, however, that the latter substance is changed to dehydro-ascorbic acid which then acts as the oxidizing agent. The particular point to be emphasized, however, is the very small effective quantity for each of the various substances listed; and it should be noted that if more than one improver is used correspondingly less of each substance is necessary.

In using flour improvers the miller adjusts his treatment according to the flour quality, and, in addition, he adjusts it to an average value that ensures the flour is usable by many customers. This means that the individual baker may still require to make some fine

adjustment to allow for differing fermentation conditions and other factors which affect his production. Thus it has become common to refer to substances added during bread-making by the baker as *bread improvers*. They may include the oxidizing agents added to the flour by the miller (potassium bromate is the main one utilized) and give him the extra tolerance required to assist him in planning his bread-making to a specific time table. Although by using a long fermentation period it is possible to make reasonably good bread from untreated flour, the use, for instance, of an improver, e.g. bromate, often means that fermentation time can be varied from say six or seven hours to three hours, thus giving a greater fermentation tolerance. Bread improvers also include other materials such as fat or surface active agents used to improve crumb softness of which the most common material is glycerinated fat (glyceryl monostearate).

The quantities of potassium bromate (converted to bromide on baking) used by the baker in bread improvers would rarely cause the effective amount given in Table I to be more than slightly exceeded. The simultaneous use of fat or of glycerinated fat reduces the amount of bromate necessary, thus a loaf of given weight containing 10 p.p.m. and produced from a sack (280 lb.) of flour (giving about 190 2 lb. loaves) containing per sack 1 lb. of fat or 3 oz. of glycerinated fat will be as good as, or even somewhat superior, in general properties and particularly with respect to crumb softness, to a loaf of the same weight prepared from the same flour containing merely 20 p.p.m. potassium bromate.

Exactly parallel results can be obtained by using ascorbic acid instead of potassium bromate, the quantities required being almost identical.

In the presence of glycerinated fat at the same level given above we have found that crumb colour is somewhat better in the case of ascorbic acid although this would not appear to be due to a bleaching effect but rather to a finer vesiculation of the crumb.

It is interesting to observe at this point that agene, which in addition possesses a bleaching effect, has proved the most consistent of all the improvers we have examined, there appearing to be very few flours indeed that do not respond to its action.

The use of surface active agents as bread improvers in the form of crumb softening agents has received widespread attention in the United States of America, and apart from glycerinated fats, such substances as polyoxyethylene stearate have been widely advocated. We have restricted ourselves to advocating only glycerinated fat for use in British bread. The product sold in this country as glyceryl monostearate contains from 20–34% actual monostearate, the remainder being glyceryl distearate and unchanged fat (tristearate). We have advocated the use of this material because we believe it free from any toxic hazard, and in the quantities used it has a very small effect on nutritional value, because it is not a substance foreign to the body—glyceryl monostearate is believed to be present in natural fats, cooking fat, and margarine—and because the amount necessary to soften the type of bread eaten in Britain means that each slice of bread consumed would appear to contain no more glyceryl monostearate than the fat spread on it.

It should be emphasized that there is a definite limit to the quantities of flour improvers and/or bread improvers that a loaf can withstand. Overtreatment soon shows itself and the bread quickly becomes unsaleable. Thus there need be no fear that the quantities of the various improvers mentioned in this paper will ever be greatly exceeded in practice.

In conclusion two other methods of bread improvement should be mentioned in this short survey of the problem. It will not have passed unnoticed that the process of bread-making involves many enzyme systems. It is not surprising therefore to find that if a flour has a low diastatic activity bakers use malt extracts as bread improvers. Recently in the United States of America certain fungal enzymes derived from the mould *Aspergillus oryzæ* have been developed to act as alternatives to malt products. The claim is made that they are more effective than malt products inasmuch as they can be prepared to meet the changing amylolytic and proteolytic requirements of individual flours.

Much effort has been put into the search for physical methods of bread improvement. A process recently patented and which has become known as the aeration process is the

subject of collaborative investigation by a number of official research organizations. This process involves the preparation of a batter from half the flour used in the final dough, mixing the batter under relatively high speed conditions until a toughening action is noticeable which is also accompanied by a bleaching effect. This batter is then added to the remainder of the flour and the dough obtained on mixing fermented in the normal way. The results are good, although in my view bread improvers would still be essential to the baker and there are a number of practical difficulties requiring further investigation. It is likely that certain enzymes, i.e. oxidases, naturally present in flour play a considerable part in the efficiency of this process.

Dr. T. Moran (Director of Research, Research Association of British Flour-Millers):

Some of the Chemical Reactions Involved in Flour Improvement

The first point I want to stress is the *relatively* small amounts of these chemical improvers that are used in flour.

TABLE I

Average Levels of Improver Treatment (Flour)		
Nitrogen trichloride	60	p.p.m.
Chlorine dioxide	30	,,
Potassium bromate	20	,,
Ascorbic acid	20	,,
Ammonium persulphate	160	,,

Some Other Permitted Additions to Food			
Food	Addition	Limit	
Cornflour	Sulphur dioxide	100	p.p.m.
Jam	,, ,,	100	,,
Sausages	,, ,,	450	,,
Coffee extract	Benzoic acid	450	,,
Cooked cured meats	Sodium nitrite	200	,,
Margarine	Boric acid	2,500	,,

For comparison I have included a list of some of the chemicals that can be added to other foods and the limits prescribed by law. I am not suggesting that the comparison is of any scientific value but it does help us to keep the flour improver problem in its proper perspective. With flour, too, the limits indicated cannot be greatly overstepped otherwise the loaf is ruined.

Vitamin C is unique because it is a reducing agent. It has, however, been shown that it is first oxidized to dehydro-ascorbic acid and then acts as an improver by handing on oxygen to the dough, itself being reduced back to ascorbic acid. It thus functions as an oxidizer and in fact this is the characteristic in common of all these flour improvers—they are all oxidizing agents although some, e.g. agene and chlorine dioxide, are much more powerful oxidizers than (say) bromate or persulphate.

Undoubtedly much of the oxidizing capacity of these improvers is spent on the fat. Wheat or wholemeal flour contains about 2½% of fat whilst white flour contains about 1%. This oxidation of the fat is obvious from the tallowy linseed-oil smell of heavily treated flour. It is very similar to the smell of long-stored flour. The degree of oxidation can, of course, be shown by ordinary chemical tests.

We are not in the least clear as to the changes that take place either in the prolonged storage of flour or in its treatment by chemical improvers which are essential for better bread. It seems certain that ultimately they are concerned with changes in the flour proteins, particularly the gluten. That the gluten does change is obvious from the comparative ease (or difficulty) with which it can be washed out from untreated and treated flour. There is a good deal of evidence to show that these changes in the gluten are connected with oxidation of the –S–S– linkages probably between cysteine molecules in adjoining peptide chains. Possibly the main function of flour improvers is to achieve that critical shear between adjoining protein chains to give the optimum dough quality. Another change also occurs: glutathione—the complex of cysteine, glycine and glutamic acid—which is present in flour and particularly in high extraction flour depresses bread quality. If (say) 200 p.p.m. of this pure substance are added to flour, the resulting bread has a poor volume, a coarse, tough, open structure and is relatively inedible. An additional function of flour improvers therefore is to neutralize any free glutathione.

Flour is such a complex system that we might reasonably expect changes to take place, over and above those required for the improvement of baking quality, when it is treated with

improvers. The fact that they are oxidizing agents suggests many possible reactions with the individual amino-acid constituents of the gluten, for example, including oxidation products of tryptophane, cysteine, methionine, serine and threonine; with free or available chlorine there is a possibility that some of the amino-acids, e.g. tyrosine, will be halogenated. Certainly with an improver such as agene or chlorine dioxide many of the constituents of flour will compete for its attention and it is reasonable to assume that a wide variety of end-products will be formed although many of them will be present in infinitesimally small quantities. It is, however, important to view this problem in its proper scale. For example, if in the agene treatment of flour all the gas went for (say) methionine—which of course it does not—the actual amount of methionine so changed would still only be 3% of the total methionine in the flour.

Mellanby's observation on the production of canine hysteria by agenized flour demonstrated in dramatic fashion this possibility of extraneous substances being formed. He found that such flour when fed in large quantities to dogs gave them running fits. At St. Albans we at once went into this problem, isolated the substance responsible and showed it was methionine sulphoximine—an oxidation product of methionine with an additional –NH grouping attached to the S atom.

This sulphoximine produces toxic symptoms in a number of animal species but so far it has not been shown to be in any way harmful to man. This perhaps is not surprising if only because of the very small amount ingested apart altogether from any differences in detoxication mechanism. In ordinary commercial flour we have found that the amount of the sulphoximine is about 2 p.p.m. so that *in the course of a year* man consumes about 2·5 mg./kg. of body-weight. The monkey by comparison requires *a single* dose 200 times this amount of the pure substance to show toxic symptoms.

TABLE II.—CRITICAL TOXIC DOSES OF METHIONINE SULPHOXIMINE

Species	Dose: mg./kg.
Rabbits (orally)	1–2
Ferrets	2
Dogs	3–5
Mice	150–200
Rats	250
Monkeys (injection)	300–500
Average consumed in one year	
Man	2·5 mg./kg.

Nevertheless it has been decided to discontinue the use of agene and all concerned are now busily engaged in deciding what shall replace it.

In America and Canada chlorine dioxide has already replaced agene and the extensive research carried out in the U.S.A. has given no reason to suspect that it could be in any way harmful to man or any animal. Nevertheless feeding tests in particular have their limitations—they are not always easy to plan unless you know what you are looking for—and therefore to clinch the matter further and leave nothing to chance, research has been going on in the laboratories I direct—the Research Association of British Flour Millers—for the past two years in an attempt to identify some of the trace substances which are formed when flour is treated with these different improvers. It is not easy research because these trace amounts are submerged in rather an intractable medium, but I believe their identification and a study of their effects on selected enzyme systems may be even more informative than *ad hoc* feeding experiments.

Dr. A. C. Frazer (Professor of Pharmacology, University of Birmingham, and Consultant Pharmacologist to the Birmingham United Hospitals):

The Medical Risks for the Consumer and How They Can Best Be Minimized

The addition, for technological purposes, of natural substances out of their normal dietary context, or synthetic chemicals to bread, is attended by some potential risk to the consumer.

The additive might have a direct or an indirect deleterious action. The direct toxic effects, both acute and chronic, can be accurately assessed by properly designed biological tests. Knowledge of the chemical, physical and biochemical properties of the substance is necessary for the effective planning of these experiments. Thus the mechanism and rate of absorption and elimination of the substance and the nature of any metabolic products must be determined. This basic information forms the foundation for the design of the experiments which are planned to assess the significance of any potential deleterious action. The investigations must be carried out in several different species and the long-term tests should be run through a number of generations. Provided cumulation can be excluded and the biological tests show hundredfold acceptability—that is, no significant difference between the test and control groups when the test substance is administered at a dosage level 100 times the standard dietary dose—the risk of direct toxic action can no longer be regarded as significant (Frazer, 1951).

There are two types of indirect toxic effect—the destruction of essential nutrients and the formation of toxic substances from other bread constituents. The destruction of essential nutrients in bread is only important if the consumer relies upon bread as a significant source of this particular nutrient. This type of action is readily assessed by direct measurement of essential nutrients by appropriate chemical or biological methods of assay. The formation of known toxic substances may be studied chemically, but the possible effects of unknown toxic agents can only be estimated biologically. The experiments are essentially similar to those used for the study of direct toxic action, but instead of giving the food additive itself, or its immediate derivatives, these substances are reacted with other bread constituents and the products of this reaction are studied. Over-treatment of flour or bread is commonly employed in such experiments, with a view to increasing the concentration of any toxic substance that might be formed. It is important to remember, however, that bread made with overtreated flour is practically uneatable and that it is logically unsound to compare artificially aged flour which has been grossly overtreated chemically and rendered unusable with normally aged or aerated flour—they are, of course, quite different. Finally, the amount of toxic substance produced is important. All chemical substances have effective and ineffective dosage levels; potent poisons, such as arsenic, are consumed daily in food without ill-effect because the dosage level is outside the effective range. Clearly, the mere presence of some toxic substance may be of little significance; the maximum dosage level in relation to body weight that may be consumed and the relationship of this level to the effective dose of the substance are matters of great importance.

Flour Bleachers and Improvers

A representative selection of the most important flour bleachers and improvers is listed in Table I. It will be seen that two of these five substances are gaseous, three are halogen-

Table I

	PPM	Properties	Bleaches	Improves	Residue in bread
Nitrogen trichloride ..	60	Gas	+	+	None
Chlorine dioxide ..	30	Gas	+	+	None
Benzoyl peroxide ..	15	Solid	+	−	Benzoate
Potassium bromate ..	20	Solid	−	+	Bromide
Ammonium persulphate	160	Solid	−	+	Sulphate

containing, and two contain nitrogen. The amounts used in flour treatment are small and only the solid substances leave any appreciable residue in the bread. With such small quantities the dangers of direct toxic action are negligible—for example, the level of bromide left in bread after bromate treatment is rather less than that usually found in tomatoes (Jacobs, 1944) and not much more than the normal blood level. On the other hand all these substances clearly cause changes in bread proteins and pigments, and there is an obvious possibility of indirect effects.

All the substances under consideration are oxidizing agents which might affect a number of dietary essentials, as shown in Table II. The most oxidizable substances present in bread

TABLE II

Dietary essential	Oxidizability	Effect on food
1. Essential amino-acids:		
(*a*) Sulphur-containing ..	+++	Changed structure
(*b*) Aromatic	++	Discoloration
(*c*) Aliphatic	+	—
2. Essential fatty acids:		
Linoleic and linolenic acids ..	++	Rancidity
3. Vitamins:		
A	+++	—
B group*	—	—
C	+	—
D*	—	—
E	+++	—
K*	—	—

*Can be synthesized by intestinal bacteria or in the body.

are methionine, and vitamin E. These will be affected first and it will be noted that more extensive oxidation, involving aromatic amino-acids or unsaturated fatty acids, causes changes which make the flour unusable. Normal treatment with any of the agents listed has not been shown to cause any change in the level of essential nutrients, with the exception of methionine, which may be decreased by 20% after heavy treatment with chlorine dioxide (Allison *et al.*, 1950). Present evidence indicates no serious loss of nutrients due to the action of bleachers and improvers at normal treatment levels.

The known toxic substances which might be produced by these additives are methionine sulphoximine and fatty acid peroxides. The former can be demonstrated by chromatography (Campbell *et al.*, 1951). It is only formed by the nitrogen-containing agene (nitrogen trichloride) and not by the other members of this group. Formation of fatty-acid peroxides in significant amounts by flour bleachers and improvers has not been demonstrated. Methionine sulphoximine has been shown to cause electro-encephalographic changes and running fits in dogs, rabbits and ferrets (Mellanby, 1946, 1947; Moran, 1947; Newell *et al.*, 1947). It causes no demonstrable effects in rats or monkeys at any reasonable dosage level. No deleterious effects or electro-encephalographic changes occur in man after administration of methionine sulphoximine (Pollock, 1949; Erickson and Gilson, 1948). Suggestions that the increase in certain diseases might be attributed to the use of agenized flour are entirely without foundation; precisely similar changes have been observed in New Zealand and other countries where agenized flour has never been used. There has been a striking improvement in the general health of people of Great Britain during the last quarter of a century, during which time nearly all the bread consumed has been made from agenized flour. The fact that the toxic effects of agenized flour on dogs was discovered accidentally some years after it had been in general use for bread-making has been used, quite illogically, as an argument against the value of animal tests. In fact, the toxic effects of agenized flour were demonstrated by biological experiment and would unquestionably have been observed in the first place if the original tests had been carried out along classical pharmacological lines, using the usual range of laboratory animals. The lessons to be learnt from the experience with agene are the vital need for active research in scientific fields relevant to food technology, the desirability of early investigation of food additives, and the importance of the proper design of biological experiments.

Extensive biological studies have been carried out with flours treated, and overtreated, with the other bleachers and improvers and no evidence of any indirect toxicity has been found. The experiments have been mainly carried out on rats, rabbits, dogs, monkeys and human subjects (Radowski *et al.*, 1948; Arnold, 1949; Newell *et al.*, 1949; Nakamura and Morris, 1949).

BREAD IMPROVERS

In addition to flour bleachers and improvers, certain additives are used in bread-making for maintaining and improving crumb quality. Three representative members of this group of improvers are listed in Table III. They are relatively inert substances chemically, but

TABLE III.—BREAD IMPROVERS

Material	PPM	Surface active	Intestinal hydrolysis	Metabolic products	Daily dose in man mg/kg.	Acceptability tests: Acute mg/kg.	Acceptability tests: Chronic mg/kg.
Glyceryl monostearate ..	500	+	+	Glycerol* Stearic acid*	7	5,000	2,000†
Stearyl tartrate‡.. ..	200	+	–	Stearyl alcohol* Tartrate*	3	5,000	1,000†
Polyoxyethylene stearate	2,500	+	++	Polyols Stearic acid*	35	5,000	2,000†

*Occur naturally in the animal body. †Include "life-span" and multigeneration tests.
‡Patented in Great Britain.

possess surface active properties. They are used in greater amounts than the flour improvers. The most likely risk with these substances would seem to be direct toxic action or cumulation.

However, in the experimental studies at present available, these substances show hundred-fold acceptability (Frazer, 1952). No indirect effects are observed when normal treatment levels are used, but high levels of treatment may interfere with the palatability of the diet. Grossly excessive amounts of polyoxyethylene stearate—some workers have used as much as 15% of the diet—may produce some effects (Schweigert *et al.*, 1950; Wang *et al.*, 1950; Sherman *et al.*, 1950). Some of the results of these experiments are not convincing and, in any case, they have little relevance to the normal dietary use of these materials. The question of cumulation must be seriously considered. The three substances listed are all metabolized in the body and on present evidence it seems unlikely that cumulation will occur at the dosage levels proposed. No direct evidence of cumulation can be found in "life span" studies. These substances have also been administered to human subjects without demonstrable ill-effects (Jones *et al.*, 1948; Page, 1949). More extensive published data on these materials are, however, urgently required.

CONCLUSIONS

Any chemical substance added to the diet, whether of synthetic or natural origin, may cause either direct or indirect deleterious effects on the animal body. This risk can be adequately guarded against by properly designed experimental investigations, involving chemical and biological assay. None of the flour bleachers and improvers, or bread improvers, in common use at the present time has been shown to have any significant direct or indirect toxic actions at reasonable dosage levels, with the single exception of nitrogen trichloride in certain experimental animals. There is an urgent need for active research in related nutritional fields and for the thorough investigation of all food additives along the lines indicated.

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Section of Proctology

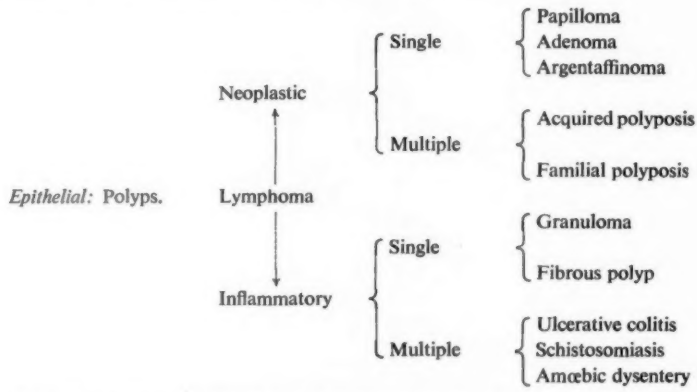
President—CLIVE BUTLER, F.R.C.S.

[*May* 14, 1952]

DISCUSSION ON THE PATHOLOGY AND TREATMENT OF NON-MALIGNANT TUMOURS OF THE RECTUM AND COLON

Dr. James Earle (The Gordon Hospital, London, S.W.1): *Short Pathological Introduction.*

The simple tumours of the rectum and colon are classified as follows:



Connective Tissue: Lipoma, fibroma, leiomyoma, angioma.

Other Tumours: 1. Dermoid cysts. 2. Implantation cysts. 3. Endometrioma. 4. Paraffinoma.

As it was impossible to deal with the pathology of all these tumours the rarer—amongst which are the connective tissue tumours—were therefore mentioned in name only.

The macroscopic and microscopic characteristics of the more important tumours were illustrated with lantern slides. Special attention was drawn to four tumours. The argentaffinoma, the lymphoma, the granuloma and the paraffinoma.

Argentaffinoma.—This tumour which arises from the Kultschitzky cells is also known as a carcinoid, argentaffin carcinoma, or Kultschitzky-cell carcinoma. They occur throughout the length of the intestinal tract. In the appendix they are slow-growing tumours which seldom metastasize; in the small intestine and colon they tend to be annular constricting growths commonly metastasizing to

local lymph nodes and to the liver. In the rectum they usually present as small rounded sessile or pedunculated tumours resembling an adenoma.

Gabriel, Dukes, and Bussey (1951) state that these tumours are not uncommon in the rectum. They have never met with one that could not be removed by local excision and their cases have had no recurrences.

Stout (1942) reviewed 10 cases of argentaffinoma of the rectum of which 2 were malignant. A large percentage of these tumours in the rectum appear to behave in a benign manner with no recurrence after local removal, and for this reason they have been included amongst the simple tumours of the rectum and described as argentaffinoma. The possibility of malignancy must always be kept in mind and these cases should receive the same careful follow-up as the doubtful adenoma.

Lymphoma of the rectum was first described by Shattock in 1890. Their importance lies in the recognition of their benign behaviour in spite of what at times may be a disturbing histological picture. In the differential diagnosis the possibility of lymphatic leukæmia or one of the reticuloses must be excluded.

Opinion varies as to whether they are neoplastic or inflammatory in origin although the majority favour the former view. Macroscopically, they present as polypoid growths varying in size from 1 cm.–9 cm. in diameter.

In the past twelve months 4 cases have been seen at the Gordon Hospital all of which arose at the ano-rectal junction in association with hæmorrhoids, the largest being 8 cm. in diameter. This association with hæmorrhoids suggests an inflammatory origin in these cases.

Granuloma.—A small tumour resembling an adenoma is sometimes seen in the rectum which, when examined histologically, is found to arise from the epithelium and to be composed of non-specific granulation tissue. They probably arise as an excessive production of granulation tissue in the healing base of a small ulcer.

Paraffinoma.—This is not a true tumour but may be mistaken clinically for a carcinoma. It results from the injection of non-absorbable oil in the treatment of hæmorrhoids. These tumours consist of cyst-like spaces containing oil, surrounded by fibrous walls and usually situated in the submucosal connective tissue.

Finally, it must be emphasized that the clinical diagnosis between the simple and malignant conditions of the rectum can be difficult and that the importance of the biopsy as an aid to diagnosis and treatment cannot be overstressed.

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Dr. Frank M. Frankfeldt (New York City): *Endoscopic Removal of Polyps by Electrosurgery.*

The important factors that will influence the technique employed in the endoscopic removal of polyps from that portion of the terminal bowel within the realm of visualization are: (1) Diagnosis, (2) Instrumental equipment available, and (3) Type of high-frequency current employed.

(1) DIAGNOSIS

The distance a sigmoidoscope will advance depends on the size and laxity of the mesosigmoid since a curved bowel is being insinuated over a straight tube. The upper limit is usually 14 in. Most polyps that can be adequately exposed are removable by electrosurgery.

The status of the polyp must be established. The pseudopolyposis of chronic ulcerative colitis and the granulomata of amœbiasis, bilharziasis and tuberculosis are recognized by sigmoidoscopy and appropriate X-ray and laboratory studies. Lesions of this type should not be removed by electrosurgery.

The location, size and type of polyp and pedicle will determine the position of the patient for operation, the length and calibre of the instrument used for exposure, the safest current to employ, and the procedure best suited for the pathological change encountered.

A. *Above the Peritoneal Reflection*

The reflection is lower in women with rectocele and cystocele, and where procidentia recti is present. In children it depends on age and size of rectum. The anterior and lateral aspects of bowel wall are the danger zones in event of perforation. The posterior surface is protected by the mesosigmoid

B. *Below the Peritoneal Reflection*

The lower 2 in. of the ampulla require a special instrument for adequate exposure

Pedunculated

The larger the polyp, the shorter and thicker the pedicle, the more liable is the tumour to be the site of malignant transformation. Darker-coloured polyps require meticulous study. The longer and narrower the pedicle, the smaller will be the calibre of afferent and efferent vessels and the tumour will be paler in colour.

Sessile

Vary from size of a pinhead to many inches (villous tumours). May be very numerous (multiple familial polyposis). Some are flat, others impinge into the lumen. All polyps warrant biopsy and microscopic study. For the biopsy of small sessile polyps the jaws or cups of the forceps must cut at the level of contact. If there is a protruding lower jaw the bite may include the entire thickness of the bowel wall and result in perforation. The Brünings' forceps is excellent for the purpose of a biopsy.

A biopsy taken from the surface or substance of a polyp, may disclose malignant transformation when the tissue is examined microscopically. If after removal the junction of the tumour and bowel wall is found to be normal by histological examination, the change in the periphery will as a rule prove to be of no serious importance. Malignant degeneration of a polyp is ordinarily of low grades. Complete local removal is apparently curative. I have never seen one instance of recurrence. Periodic examination is a routine procedure and should be continued for five years.

(2) Instrumental Equipment (Fig. 1)

The instruments in the illustrations are ample for coping with any contingency that might arise. It is important to employ the tube of the largest calibre which the involved bowel segment will admit.

For exposure.—Instruments of varying lengths and diameters must be available. Those made of bakelite or hard rubber are preferable because they do not conduct electricity. A bevel at the distal end will augment the working area (Fig. 1, 2). Good illumination is necessary and extra lamps must be within reach. The circumference of the examining tube should be involved as little as possible by the light mechanism (Fig. 1, 10). The Morgan sigmoidoscope and the author's model (Fig. 1, 1) offer this advantage.

Below the rectosigmoid.—The Strauss operating proctoscopes (Fig. 1, 2) are best suited for exposing this area. They are procurable in lengths up to 6 in. and diameters up to 1¼ in. The distal ends are bevelled. The metal tube is 5½ in. long and 1⅛ in. in diameter and has a small bevel at the distal end (Fig. 1, 3). Because the light occupies so little of the lumen, there is more room for manipulation. The hinged speculum will expose the posterior part of the lower ampulla. When the blades are fully separated the hiatus will measure 1½ in. (Fig. 1, 4).

Above the rectosigmoid.—A tube 1 in. in diameter and 10 in. long is used routinely. Some bowels will only accommodate an instrument ⅞ in. in diameter. A ½ in. to 1 in. bevel at the distal end gives that added exposure that is so important in this bowel segment.

For operation or attack.—The author's snare (Fig. 1, 7) with attachments is particularly suited for the removal of any type of polyp. It is angular in construction, so that the handle does not obstruct a view of the shaft. The two small holes near the distal end of the wire passer are for holding a snare loop of the desired size. Monel wire is best suited for snaring. It contains 30% copper and 70% nickel and is, therefore, a better conductor of electricity than steel wire. It is supple and pliant and a loop made of this material may be shaped to conform to the contour of the polyp. The loop can be tilted. For routine use, Monel wire 0·011 in. in thickness will bear any needed stress. The snare loop created can be used over and over again. For thin pedicled polyps, a finer Monel wire is available. If the snare loop is made too large, it cannot be insinuated into the shaft, and, as a result, the attacked tissue will not be completely severed. At the distal end of the wire passer, there is a screw-on arrangement that will accommodate tips of many varieties. Different-sized ball electrodes, a cutting blade and a forceps which closes over tissue like an artery clamp (Fig. 1, 6) are available. The latter

may be utilized for coagulation or sparking. Shafts of various lengths can be procured. They are fitted with wire loops and the necessary electrodes prior to operation. The tips that are screwed on the wire passer are angulated, and veer away from the shaft. The current passing through the active electrode can be directed more accurately to the target. Operative procedures are not obstructed by the shaft.

The angulated Y tube (Fig. 1, 5) is for the suction of smoke and blood. One side may be used for irrigation, and the other for controlling the negative pressure.

The tumour-grasping forceps (Fig. 1, 9) is employed for exposing the pedicle or the juncture of polyp and bowel wall (*see* Fig. 4C). It is thin-shafted and does not usurp much of the working diameter of the operating tube.

This angulated instrument (Fig. 1, 8) is manufactured in various lengths and is fitted with a ball electrode or cutting blade at the distal end. Both are employed for sparking.

The attachments, screwed on the wire passer of the snare, give this instrument all the advantages of a Brünings' forceps.

The tube (Fig. 2) shown with the Strauss proctoscope, has a small metal rim at the distal end. While the suction functions to keep the field free from blood and smoke, the metal part is utilized for sparking or lightly stroking over the bleeding area. For stroking, the medium coagulating current of a tube machine must be used. Coagulation will not be deep and there is little or no dehydration or heat production in the tissue attacked.

Adrenaline, Monsel's solution (bisulphate of iron) and oxycel should be available to control capillary bleeding.

(3) High-frequency Currents Suitable for Polyp Removal

It is a prudent plan to refer all patients with polyps to an institution that is equipped with a dependable high-frequency apparatus. Only by continued practice on raw steak, rectal mucosa (exposed during a hæmorrhoidectomy) and tumour tissue, is it possible to assay the destructive action of the various high-frequency currents suitable for this type of electrosurgery.

High-frequency currents suitable for the removal of polyps are generated either by a tube (in Great Britain called a valve machine) or a spark gap machine. Apparatus is available that will deliver both currents or a combination of the two (blended current). Most outfits only have outlets for the cutting and coagulating currents. The addition of a Oudin coil to the circuit is sufficient to produce desiccation, fulguration, and Oudin currents. Electricity of this type is generated by a spark gap machine. These currents are mono-terminal (employed without an indifferent electrode), damped, and are characterized by being of low amperage (from 200 milliamperes to 1–1½ amperes) but of high voltage (many thousands—10,000 or more for the Oudin current). Voltage represents the electromotive force necessary to bolster the low amperage and make the current function. A good example is the pressure necessary to cause water to flow through a pipe.

Apparatus generating the cutting and coagulating currents, operates at a frequency varying from 1,000,000 to 10,000,000 cycles or oscillations per second. These figures represent a maximum for a particular machine and not a variation in cycles in one outfit.

The oscillographs (Fig. 3) are from a machine operating at a frequency of 2,000,000 cycles per second. They are intended to show the difference between the coagulating current of a tube and a spark gap machine. The oscillations of the latter take place like the pendulum of a clock, swinging out at full range, then swinging less and less in amplitude until they die out. It is akin to the sound produced by striking a bell. The noise is loudest at the moment of impact and gradually becomes silent. The differences between the two currents are as follows:

Tube Current (Cameron)	Spark Gap Current
Low amperage (2½ amps.)	High amperage (7–14 amps.)
Current amplitudes are even and equal	Amplitudes are uneven and intermittent
Comparatively cold current	Hot current (27 times hotter than Cameron)
Zone of coagulation 1–5 mm. maximum. Since ½ ampere used with snare technique, only about 1–1½ mm. coagulation	Much deeper coagulation zone
Very little or no dehydration	Considerable dehydration
Must count 10 while cutting through average pedicle	½ to 2 seconds
No danger of perforation	Danger of perforation if current contact is prolonged
Wound healing fast, five to seven days	Slow healing, two weeks or more

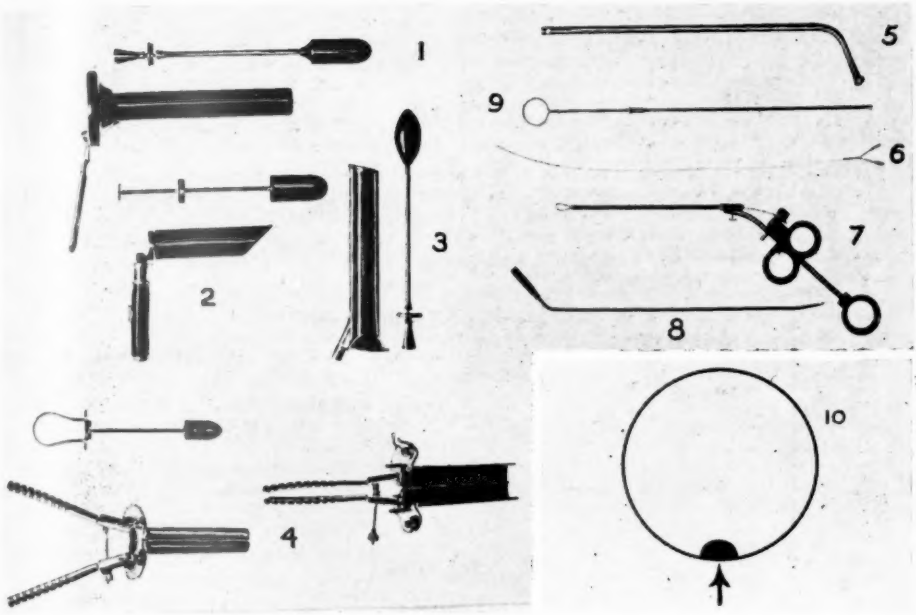


FIG. 1.—Instruments for exposure and operation, 1–9. The lamp (10) involves very little of the working lumen.
1, Author's operating sigmoidoscope. 2, Strauss' operating proctoscope (note bevel at distal end). 3, Author's operating proctoscope. 4, Hinged operating proctoscope (Author's). 5, Angulated tube for suction and irrigation. 6, Forceps arrangement on wire for Author's snare. 7, Author's snare. 8, Angulated insulated instrument for sparking. 9, Tumour-grasping forceps (modified by Author). 10, Showing small amount of circumference involved by lamp in Author's sigmoidoscope.

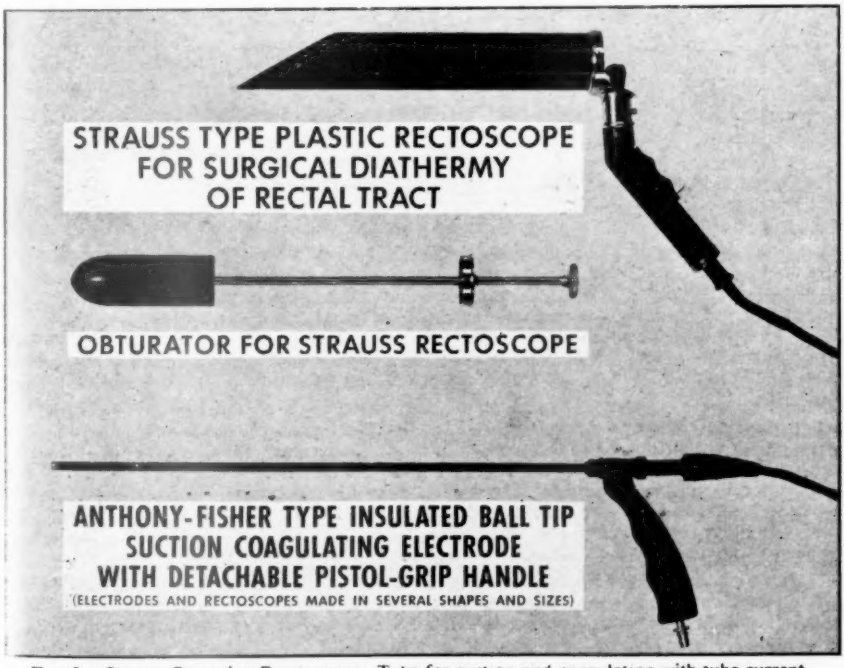


FIG. 2.—Strauss Operating Proctoscope. Tube for suction and coagulation with tube current.

The difference between a coagulating and a cutting current is that in the former there are 3½ to 4 wave-lengths in a given period, whereas in the latter there may be 15 to 40 in the same elapsed time. Altering the amperage output of the machine will not change the number of wave-lengths.

The current density is greatest at the tip of the active electrode. The destructive action will depend on several factors, viz. (1) the amplitude (amperage) and type of current employed, (2) the size and the shape of the active electrode, (3) the resistance of the pathological process (thickness and how profusely supplied with blood), (4) whether or not the electrode is in contact with the tissue treated.

Cutting current.—The cutting current of a tube machine is never employed in polyp removal.

The graded or slow-cutting current of a spark gap apparatus is a comparatively safe medium for snare techniques. For ordinary electrosection, a reading of 32 on the old Jr. Bovie has been found most satisfactory. For polyp removal with the snare loop, a reading of 19 is adequate. The machine output at that grading is 2½ to 3 amperes, and the zone of coagulation produced in the tissue attacked

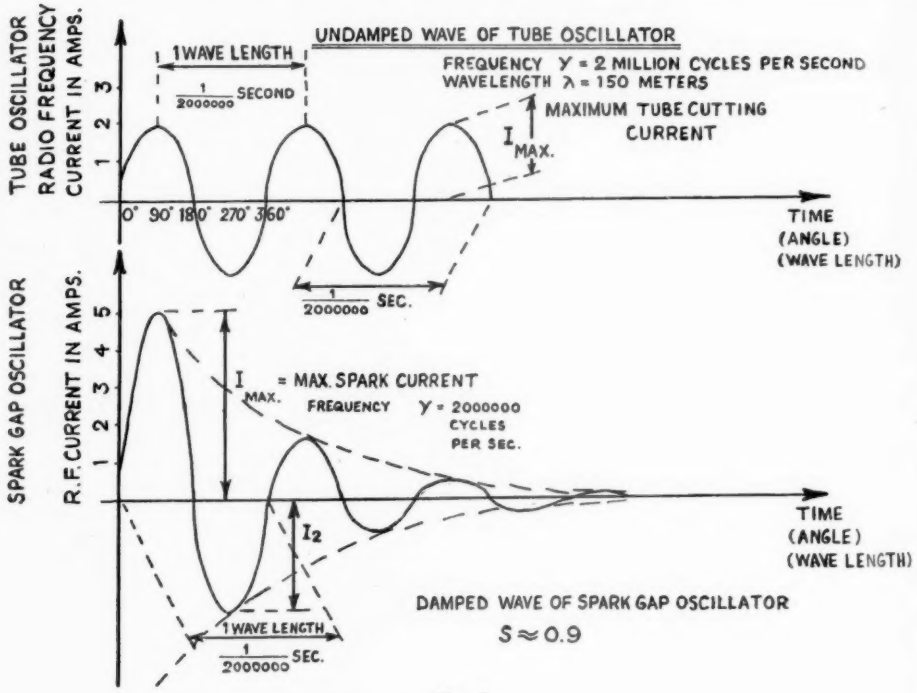


FIG. 3.

varies from 1½ to 3 mm. If the active electrode is not held in contact with the area treated for too prolonged a period, the depth of coagulation, dehydration, and heat production is within safe limits and there need be no concern about secondary hæmorrhage, or bowel perforation. Very little smoke is created during the operation of this current. Experience will teach one how quickly to close the snare loop.

Coagulating current.—Tube machine: The medium or moderate coagulating current is theoretically perfect for polyp removal by a snare procedure. At that reading the machine is delivering about ½ ampere of current. The area of coagulation is usually 1–1½ mm. There is little or no dehydration or heat production in the tissues. It is a slow-acting current and hence 10 to 20 seconds must transpire while the snare loop is being closed. If this time element is disregarded, severe bleeding may occur. Smoke generated is cleared with suction. The metal-rimmed suction tube, activated with the same current, is employed for stroking a bleeding area.

The coagulating current of a tube machine will not produce a spark.

Spark gap apparatus: For deep coagulation a large ball or disc electrode is employed. Either type is placed in contact with the tissue to be destroyed and only then is the current turned on. This avoids sparking. The action on tissue is to create a zone of coagulation equal in size to that of the active

electrode. Theoretically, the square of the current equals a certain indefinite area of coagulation. After a variable period (depending on the size of the active electrode and current amplitude) carbonization occurs and an insulated barrier is created. The electrode coming in contact with this zone begins to spark. To continue the destructive action of the current, it is necessary that this charred debris either be curetted or cut away.

While coagulation is going on the tissue is actually "stewing in its own juice". There is a bubbling and seething in the involved area. The depth of coagulation, dehydration and heat production depends on the size of electrode and the period of current activity. Considerable smoke is created and the field must be kept clear by suction.

High-frequency sparking.—The high-frequency spark is a very valuable adjuvant for the removal of polyps and the control of bleeding. The length and type of the spark created are controlled by the amplitude of the current employed (amperage). Those generated by a *Oudin coil* (desiccation, fulguration and Oudin) vary from $\frac{1}{32}$ in. to 1 in. or more. (The Oudin generates the longest spark, the desiccating current, the shortest.) Because of the very low amperage but high voltage, the action of these sparks on tissue is very superficial and there is little or no heat created in the area bombarded. These sparks will destroy small flat sessile polyps or control the capillary ooze following polyp removal. For more intense action other currents are necessary.

The spark generated by the bipolar coagulating current of a spark gap circuit can also be graded by changing the amperage. It is advisable to begin with a small spark and increase to the desired size and intensity by "jacking up the current". After a short period carbonization occurs and the current is neutralized by the insulated barrier created. Here again, curetting and cutting of the charred area is necessary before the sparks will function again. Sparks from the bipolar coagulating current create a zone of coagulation, dehydration and heat production in the tissues that is circumscribed. The extent and depth of this area will depend on the size of the active electrode, the current amperage, and the length of time the latter is performing.

Monopolar coagulating current.—When the monopolar coagulating current is employed for sparking, because the active electrode is not in contact with tissue, the electric arc is broken. It will require greater current amperage and voltage to equal the effect on tissue produced by a biterminal coagulating current. The sparks from a monoterminal coagulating current will destroy polyps up to the size of a large pea, and will control all but the arterial bleeding following polyp removal. An attempt must be made to delay as long as possible the formation of the carbonized zone.

Conclusion.—The medium coagulating current of a Cameron tube machine is safest for cutting through small polyps or pedicles. The snare loop must be closed slowly, 10–20 seconds. The slow-cutting current of a spark-gap machine is also a safe medium for a similar function. There is, however, less likelihood of bleeding during the operation and the field is not obscured by smoke.

(4) Operative Procedures

Pre-operative.—(1) *Catharsis:* The bowel is best cleansed with saline laxatives administered for two days prior to operation. Four hours before the patient goes to surgery, a pint of warm water is injected into the bowel. This is sufficient to empty the ampulla of the rectum.

(2) *Medication:* Where general or intravenous anæsthesia is employed, a hypodermic of 100 mg. of Demerol and 1/150 grain of atropine sulphate is injected. When local infiltration analgesia is the method of choice, the patient receives $\frac{1}{2}$ grain of Luminal half an hour before going to the theatre. Children are given smaller doses of these drugs. Atropine is necessary because ether is employed.

(3) *Anæsthesia:* Since I advocate the use of the largest calibre tube that the involved segment of the bowel will admit, some form of anæsthesia is necessary. For the majority of cases, local infiltration analgesia with eucupine and procaine suffices. It has the added advantage of prolonged action. For the highly strung, emotional patient, intravenous anæsthesia with sodium Pentothal, using the drip method, has given satisfactory results. In children, ether anæsthesia is necessary. If a large broad-based polyp is to be removed, profound relaxation of the anal musculature is necessary. A low spinal, saddle-block type of anæsthesia will give the desired effect.

(4) *Position of patient:* The semi-inverted jack-knife position is preferred by many proctologists. The aged and infirm, cardiacs and asthmatics find this posture intolerable. It is natural to have the patient assume an attitude which will offer maximum exposure of the pathological process. I have found the left lateral prone and knee-chest positions satisfactory for the majority of cases. When a polyp is encountered in the lower 2 in. of the ampulla posteriorly, the lithotomy position is advisable, because a special instrument is required for adequate exposure.

(5) *Survey of instrument equipment.*—(*a*) Check electrodes to patient and machine. (*b*) Test suction apparatus. (*c*) Synchronize the spark gaps, if that type of machine is to be employed. (*d*) Inspect the array of instruments available and prepare snare loops to conform with the size and contour of the polyp. (*e*) Practise on raw meat to make certain that the current is being delivered to the active electrode and note the destructive action of the various currents to be employed.

Operative.—The patient is placed in the position best suited for exposing the pathological process. The largest calibred instrument the involved bowel segment will admit is inserted. In a description of the techniques employed, all snare procedures will be performed by activating the loop with the slow-cutting current generated by the old model Jr. Bovie machine at a reading of 19. If the tube coagulating current is utilized, it will be so stated.

A ball type of active electrode is employed for sparking procedures and is held from $\frac{1}{16}$ to $\frac{1}{8}$ in. from the area treated.

Below the rectosigmoid.—Divulse the anal musculature sufficiently to readily admit the examining tube. A Strauss operating proctoscope, $5\frac{1}{2}$ in. long by $1\frac{1}{4}$ in. wide with a bevel at the distal end is used for exposing the polyp and pedicle if present. The bevel increases the working area to $1\frac{1}{2}$ in. in length. Excellent illumination is furnished with the Cameron light.

Sessile polyps: Small flat sessile polyps are destroyed by mono- or bi-polar sparking produced by the desiccating, fulgurating, Oudin or coagulating current. A ball electrode is employed. If the growth is about the size of a pea and impinges into the bowel lumen, it is removed with a snare loop, closing quickly. The mucosal base is included. The zone of coagulation will be about the thickness of a human hair. The specimen is unimpaired for microscopic study.

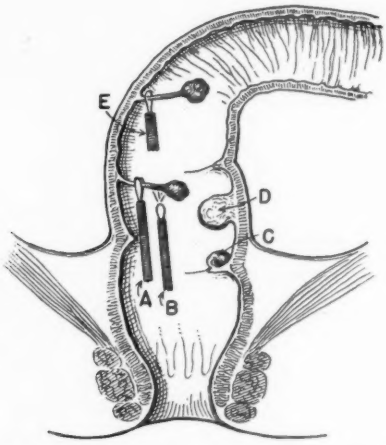


FIG. 4.—Elective procedures for polyp removal.

The larger sessile polyps Fig. 4, D (up to the size of a grape) may be removed with a snare loop cutting at the level of the bowel mucosa, and then lightly sparking the base. The tumour may also be coagulated, using a large ball or flat active electrode. The shrivelled mass is then severed at the level of the bowel wall with a snare technique. Another method is to remove the polyp piecemeal with a multi-snaring operation and then coagulate the remaining stump.

Pedunculated polyps: Fig. 4 demonstrates techniques that are employed for the removal of pedunculated polyps.

(1) The pedicle is snared at its juncture with the bowel wall using a loop that is activated with the slow-cutting current. The rate of snare closure will depend on the thickness of the tissue to be severed.

(2) The pedicle (Fig. 4, E) is ablated with the snare loop a short distance from the bowel wall, and the remaining stump destroyed by sparking with the graded mono- or bi-polar coagulating current.

(3) The pedicle (Fig. 4, B) may be sparked a short distance from and up to the bowel wall, until it turns a greyish white. The snare is then applied to the pedicle close to bowel wall and closed quickly.

(4) The diathermy forceps (Fig. 4, A) embraces the pedicle a short distance from the bowel wall and then the graded coagulating current is sent through until there is the proper change in colour. The current has a spreading action that will extend to the bowel wall. The afferent and efferent vessels are sealed. The snare loop is then employed to cut the pedicle at the mucosal level, closing in $\frac{1}{2}$ to 1 second.

Above the peritoneal reflection.—Sessile and pedunculated polyps in the rectal ampulla above the peritoneal reflection are more readily removed than those in the sigmoid because large-calibre bevelled tubes may be used for exposure. The rectal mucosa is thicker and rugose in this region.

Sessile polyps: Small sessile polyps are destroyed by sparking, using a ball electrode. This may be accomplished in one or several sittings. Sessile polyps up to the size of a grape, located in the ampulla, can be severed at their juncture with the bowel wall or removed piecemeal, and the base coagulated carefully by sparking. If removed fractionally, the outer aspect of the tumour is snared with the coagulating damped current at a reading of 60–70. If broad-based tumours occur in the sigmoid, abdominal section and sigmoidotomy is the advocated procedure.

The rectal ampulla is the usual site for villous tumours. The majority of these can be pulled down, transfixed in section and excised.

In a recent survey Sunderland and Binkley (1948, *Cancer*, **1**, 184) state that "68·7% of the papillary adenomas showed areas of cytologic carcinoma, either in the original tumour, or in a recurrence at the site of removal; 39·5% developed invasive carcinoma. When carcinoma occurs, it may appear in any part of the papillary adenoma; it shows no special predilection for surface or base".

Papillary adenomas in the rectum below the peritoneal reflection are removable by mass coagulation with disk and large ball electrodes and a multiple snare technique. A stump about ⅜ in. should remain after the charred tissue is cut away. This residuum is carefully sparked or grasped in successive areas by the diathermy forceps which is then charged with the coagulating spark gap current. It is a time-consuming procedure and there is the great hazard of primary and secondary hæmorrhage. Patients should be typed before operation, so that in the event of severe bleeding transfusion is not delayed.

Since a conservative resection will cure these patients and the incidence of malignant transformation is so great, it does seem the wiser plan to resort to radical measures in the larger papillary adenomas.

Above the rectosigmoid.—Pedunculated polyps: Techniques are similar to those employed for the removal of tumours below the rectosigmoid. The safest procedure is to spark the pedicle a short distance from and up to the bowel wall until the colour becomes greyish white. The snare loop is then applied to this coagulated area and closed in about ½ to 1 second.

Large sessile tumours located in the sigmoid or those with a pedicle thicker than a lead pencil should be removed by abdominal operation. It is a safer procedure. Because of the size of the pedicle there is a greater possibility of malignant transformation.

The coagulating current is not intended for cutting tissue. If it is employed for this purpose, the snare loop must be closed slowly. If the damped spark gap current is chosen, the prolonged contact of active electrode (snare loop) and the pathological process will naturally result in a considerable area of coagulation, dehydration and heat production in the area treated. The use of a biterminal coagulating current to snare off a polyp flush with the bowel wall is a dangerous procedure particularly if the operation must be performed above the level of the peritoneal reflection. The medium coagulating current generated by a Cameron tube machine, or the slow cutting current of a spark gap apparatus, is safer for the purpose.

Good exposure, ample light, and the proper current delivered to the target by an active electrode that does not obstruct the view, will permit removal of polyps with a minimum degree of hazard to the patient.

Complications

Errors in technique are responsible for the complications that occur:

(1) Incomplete removal of the tumour is due to snaring at an improper level or incomplete destruction by sparking.

(2) Hæmorrhage. (*a*) Primary: The active electrode was not activated with the high-frequency current during the operation (cold snare). (i) Closing the snare loop too quickly. (ii) Use of improper current.

(*b*) Secondary: Secondary hæmorrhage usually occurs from the fifth to the tenth day postoperatively and is due to deep coagulation, dehydration and an extensive zone of heat production in the bowel wall. Necrosis and slough separation are responsible for the opening of a vessel. It occurs when a coagulating current is employed and the active electrode contacts the bowel wall for too prolonged a period.

(3) Perforation—Peritonitis. (*a*) The cause is the same as for secondary hæmorrhage except that the necrosis extended to involve the peritoneum.

(*b*) By undue traction on the pedicle the peritoneum is invaginated and cut when the pedicle is snared.

(Space will not permit a discussion of these unpleasant but avoidable complications.)

Case Report

Mr. Z., 52 years old, Case No. 248465, was admitted to the Bronx Hospital on March 28, 1952, with a history of bleeding from the rectum for several months.

Examination revealed a sessile polyp, the size and shape of a large grape, 5½ in. from the anal verge on the right posterolateral aspect of the bowel wall (*See* Fig. 4, D). A second polyp, the size of a pea, was disclosed 3 in. from the anal verge on the anterior surface of the ampulla. X-ray of the colon did not demonstrate any other pathological change.

Operation was performed on March 29, 1952. The anal musculature was relaxed with local infiltration anæsthesia. The anal canal was divulsed sufficiently to admit a Strauss operating proctoscope, 5½ in. long and 1¼ in. in diameter. There was a 1½-in. bevel at the distal end. The grape-sized polyp was removed at its junction with the bowel wall using a snare loop, activated with the slow-cutting current. There was no bleeding. The smaller, pea-sized polyp and its mucosal base were removed with the snare loop, employing the same current.

Bowel action was permitted on the fifth post-operative day and Mr. Z. was discharged from the Bronx Hospital on April 5, 1952.

Microscopic diagnosis. Slide Path. No. 47593 (Figs. 5A, B and C).—Section of intestinal tumour reveals large, bizarre papillary neoplastic glands with occasional multi-acinar formation. In one area a large group of these glands has broken through the muscularis mucosa into the underlying connective tissue. The glands are well

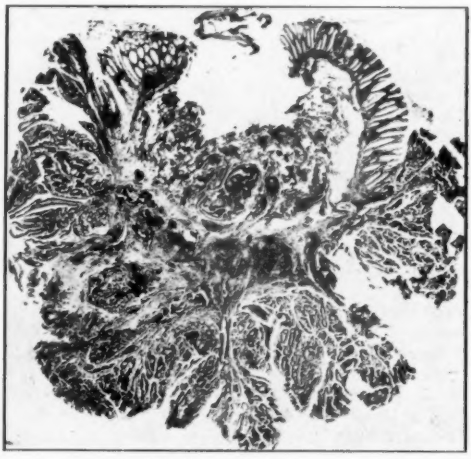


FIG. 5A.—Sessile polyp. Snare removal with slow-cutting current by Dr. Frankfeldt, 1952. (No. 47593.) Low-power view of whole tumour. × 7.

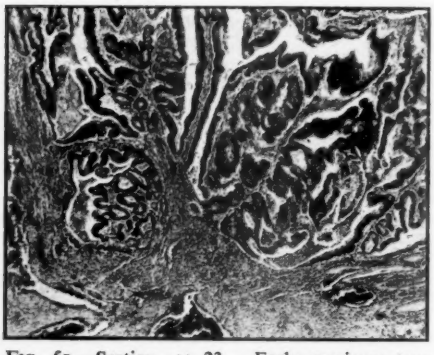


FIG. 5B.—Section, × 23. Early carcinomatous invasion of stroma of polyp.

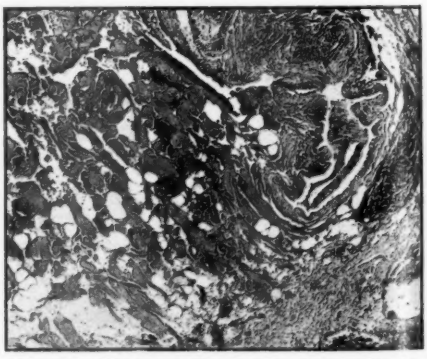


FIG. 5C.—Section, × 33. Portion of base of polyp showing coagulation and necrosis of tissues by the slow-cutting current.

differentiated and show multi-layering and frequent mitosis. The stroma is markedly congested, hæmorrhagic in area and infiltrated by a moderate number of round cells and polymorphonuclear leucocytes. Supplementary report to follow on second polyp. Local removal indicated with monthly follow-up.

Diagnosis (Joseph Felsen, M.D.).—Polypoid adenocarcinoma of large intestine, grade I, borderline grade II. Secondary polyp was diagnosed as simple adenoma.

Mr. Z. was sigmoidoscoped three weeks after operation and the involved areas were completely healed. If any malignant cells had remained in the bowel wall under the area where the large polyp was removed, complete healing would not have taken place because the tumour tissue still existed.

I am indebted to Dr. Cuthbert Dukes for the excellent photomicrographs. They are self-explanatory. Dr. C. Spaeth, of the American Cystoscope Makers, Inc., of New York, very generously provided me with the oscillographs demonstrated.

SUMMARY

(1) A tube of the largest lumen that the involved bowel segment will admit is recommended for exposure-operation.

(2) High-frequency currents employed in electrosurgery have been contrasted.

(3) The medium coagulating current from a tube (valve) machine (Cameron) and the slow-cutting current generated by a spark gap machine have been found safest for the snare removal of polyps. The use of a biterminal, damped, coagulating current for procedures close to the bowel wall, if the lesion is located above the peritoneal reflexion, is not recommended because ot the danger of perforation.

(4) Techniques have been described for the endoscopic removal of polyps by electrosurgery that offer the least hazard to the patient.

Mr. H. E. Lockhart-Mummery: *The Management of "Benign" Adenomas found Histologically to be Early Carcinomas.*

At St. Mark's Hospital Dr. Cuthbert Dukes and I have recently been investigating the problem of the malignant polyp, or more precisely the fate of patients from whom a polyp has been removed by local excision and in which malignant change is found to have occurred. Our results will be published in more detail in the *Lancet*. We found that between the years 1933 and 1949 47 cases, classified in our records as cancer, had been treated by local excision. These were all certainly malignant, either in whole or in part, and most of them were clinically benign tumours in which the malignant change was only discovered on microscopical examination. They were all solitary tumours, and all adenocarcinomas arising from the rectal mucosa, and have all been followed up for at least two years. I would like to thank all my senior colleagues at St. Mark's for their courtesy in giving us access to their case-records.

We have reviewed the sections of these cases, and found, as might be expected, that the prognosis after local excision seemed to depend both on the extent of spread and on the histological grade of malignancy. The histological grading of rectal tumours into those of Low, Average, and High grades of malignancy has been Dr. Dukes' practice for many years, and his writings on this subject are well known, but in discussing the extent of the malignant change in these pedunculated tumours certain terms which I shall use require description.

We found that the malignant change in a polyp may be encountered at three stages:

(1) *Carcinoma in situ.*—Here small foci of carcinoma of microscopic dimensions are found, with no evidence of infiltration or invasion. The detection of such lesions and the interpretation of the histology requires considerable experience on the part of the pathologist, and there may often be an element of doubt as to malignancy. Though we regard such cases as malignant, they have not hitherto been classified in our records as cancer, and no such cases are included in our series of 47.

(2) *Focal carcinoma.*—As areas of carcinoma in situ grow and coalesce, a larger lesion results which is now undoubtedly malignant, though still almost completely confined to the region of the mucosa. Such a lesion we have called "focal" carcinoma.

(3) *Invasive carcinoma.*—If the microscopic section shows evidence of spread of the malignant process either into the stroma of the polyp, down the stalk, or into the bowel wall, we regard the tumour as invasive in character.

(Slides were shown to illustrate these stages, both by diagrams and from actual sections.)

To turn now to the results of treatment, there were 17 cases in our series of 47 which we regarded as focal, and the results of local excision in these cases were entirely satisfactory. One patient died of intercurrent disease, but the other 16 are alive with no evidence of recurrence. All these cases were of low or average grade malignancy, and there was no focal carcinoma of high-grade malignancy in our series. I think we may conclude that local excision seems to be curative for these focal carcinomas when the malignancy is of low or average grade—I doubt if it would be equally safe should a focus of high-grade malignancy be seen.

I think we may also justifiably conclude that if these "focal" tumours have responded so well to local excision, then tumours at an even earlier stage of development, that is to say carcinomas in situ, should have an equally good prognosis after such treatment; and we do not believe that a report stating "carcinoma in situ" should be an indication for radical surgery.

In dealing with the results of the invasive carcinomas, we found that the histological grading was an important factor. The results were satisfactory in those cases of Low-grade malignancy; there were 7 such cases, 1 of whom had a restorative resection and no residual carcinoma was found in the specimen; the other 6 are alive with no evidence of recurrence. The danger of metastasis in these low-grade cases is slight; in a group of similar low-grade cases that we examined which had

been treated by radical measures we found that in none of them had there been any lymphatic spread. So we feel that in these cases it is safe to defer radical surgery, provided that the patient is kept under close observation. The local excision may have eradicated the disease, as it seems to have done in our cases, but, if not, local recurrence will probably become apparent before dissemination.

The picture was quite different in those cases of High-grade malignancy. There were only 3 such cases in our series, but they all recurred, and when treated by radical excision for that recurrence they were all found to have lymphatic metastasis, which was extensive in 2 cases. It is obviously unwise to temporize in these cases, and from our knowledge of the bad prognosis usually associated with high-grade rectal cancers, it would seem that should any area of High-grade malignancy be reported in a removed polyp, it is wiser to advise immediate radical surgery.

The invasive tumours of Average-grade malignancy formed the largest single group in our series. There were 20 such cases, and only 6 of them are alive with no recurrence, all 6 having been observed for over five years. 5 are dead of unrelated causes, and no less than 9 recurred. We tried to determine the first manifestation of recurrence in those patients, but in 2 of them we are ignorant as to this as they did not attend the hospital again, though we know that they were both treated later for rectal cancer. Of the other 7, 4 showed a localized nodule at the site of former excision as the first sign of recurrence; they were all treated by combined excision, and in 1 of them a near-by gland contained a metastasis, though the local recurrence in this case was confined to the mucous membrane. In the other 3, lymphatic metastasis was the first sign of recurrence, occurring in the inguinal group in 2 cases (the primary having been at the ano-rectal junction), and in the glands in the meso-rectum in the third case. In none of these 3 cases was there clinically detectable recurrence at the primary site.

In attempting to analyse these recurrences further, we tried to assess the margin of clearance of the original local excision. We found that in most, but not all, of those that recurred the margin of clearance had been small, and feel that this factor should also be taken into consideration. It is in these invasive tumours of Average-grade malignancy that the decision is most difficult for the surgeon. In view of the danger of lymphatic metastasis, we feel that it is safest to advise excision of the rectum if there is microscopic evidence of spread into the bowel wall, or where the margin of clearance round the tumour has been small. In other cases it is probably safe to keep the patient under observation.

It is only by careful assessment of all the factors concerned, extent of spread, grade of malignancy, and margin of clearance, that it is possible to plan treatment to the patient's best advantage. If it is in any way possible, I think the surgeon should remove apparently benign rectal tumours intact, and that if a focus of malignancy is found, the pathologist should give as full a report as possible with particular reference to the factors referred to above. Each case must be considered on its merits. Some cases of malignant polyps require radical surgery; others can be treated by local excision—but any patient so treated should be kept under supervision for several years.

Mr. W. B. Gabriel: *The Surgical Management of Large Villous Tumours of the Rectum.*

The tumours that come within this category might be reckoned to be those of 3–4 in. (7·5–10 cm.) in diameter or even larger, flat or protuberant or both, and covering an area of perhaps 9–10 square inches (say 70–100 sq. cm.) of the rectal wall (Fig. 1).

As a preliminary I should like to record my appreciation of the historic monograph on villous tumours of the rectum published by André Lambling (1928); it contains a shrewd and accurate appreciation of the problem, with many clinical and pathological observations which have stood the test of time. Lambling served as an interne at the Hôpital Saint-Antoine in Paris under our old friend and Honorary Member of this Section, Dr. R. Bensaude.

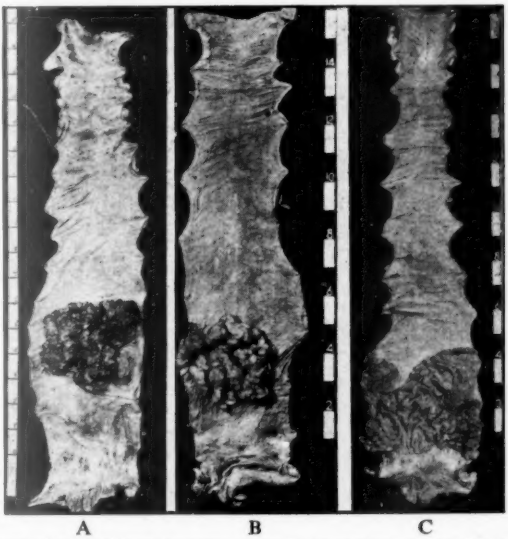
Incidence.—It is rare to find tumours of this size still benign and in my series of 980 perineo-abdominal excisions (1932–1952) there have only been 11 cases of large villous tumours in which no focus of malignant change was discovered in the pathological department at St. Mark's Hospital.

In contrast with this figure I have been informed by Mr. H. J. R. Bussey that in this series there were 98 cases in which the carcinoma was considered to have arisen in a pre-existing benign tumour, usually a villous tumour; cases of polyposis have been excluded from this calculation so it is evident that in this series approximately 1 in 10 of the cancer cases have arisen as the result of malignant change in a benign tumour and that the still benign large villous tumour is a rarity which might in fact be proved to be even more rare if it were possible to cut serial sections through these large tumours; the labour involved in doing this would, however, be immense.

Diagnosis.—The difficulty in diagnosis of villous tumours of the rectum accounts for the delay that too often takes place. These tumours are soft and impalpable and this often explains a delay of perhaps up to five years in establishing the cause of diarrhœa and mucoid rectal discharge. Even on sigmoidoscopy a villous tumour is pale (as pale as the surrounding mucous membrane) and requires careful inspection to identify it.

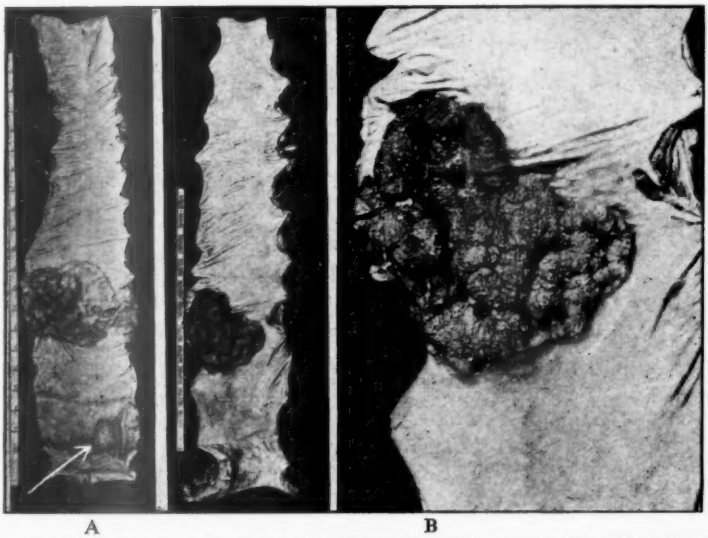
The next difficulty is to estimate the extent of such a lesion and I venture to say that this is a very

real and often an insoluble problem. The central part of a large villous tumour may be raised, prominent and palpable, but the outlying portions are often flat, soft, impalpable and really impossible to define. In one of my cases an implantation in the lower rectal third from a large villous tumour higher up was missed altogether clinically and was only discovered when the specimen was opened up after the radical operation (Fig. 2A).



A B C

FIG. 1.—Three specimens of large villous tumours removed by perineo-abdominal excision. In case marked A the patient survived for thirteen years and in B for five years eight months. C was a recurrent villous tumour which had been excised locally fourteen years previously and it now showed early malignant change; patient alive and well three and a half years later.



A B

FIG. 2.—A, large villous tumour in rectosigmoid with undiagnosed implant in lower third of rectum; patient survives over thirteen years. B, malignant change at upper extremity of a large villous tumour. Both cases treated by perineo-abdominal excision.

Malignant change is, I believe, indicated for certain if an ulcer or an indurated area is felt at any part of the villous tumour, whether central or peripheral. The difficulty is that when the tumour is large and situated in the upper part of the rectum it may be impossible to palpate evidence of malignant change at the upper limit of the tumour, much less even to feel or estimate the extent of the growth (Fig. 2B).

Biopsy.—Fragments for biopsy should be taken from any suspicious parts as indicated above, especially from any firm or friable areas that can be identified and from the edge of any visible or palpable ulcer. If the pathologist finds clear evidence of malignant change this is a definite help in deciding upon treatment, but if the report is negative or equivocal the surgeon must rely upon his

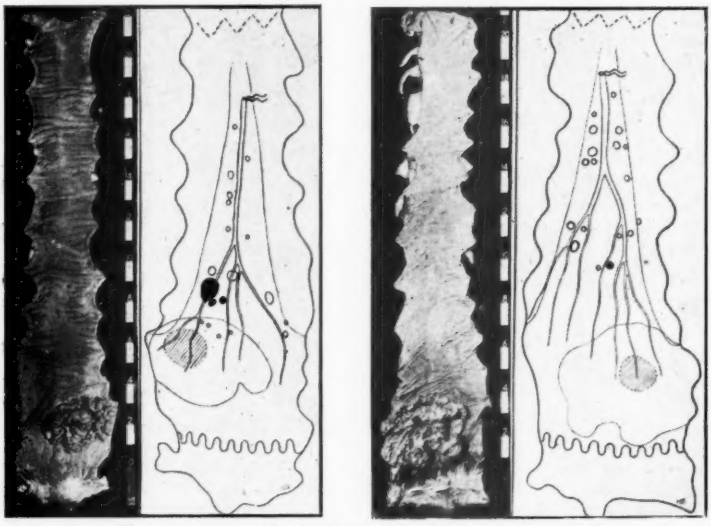
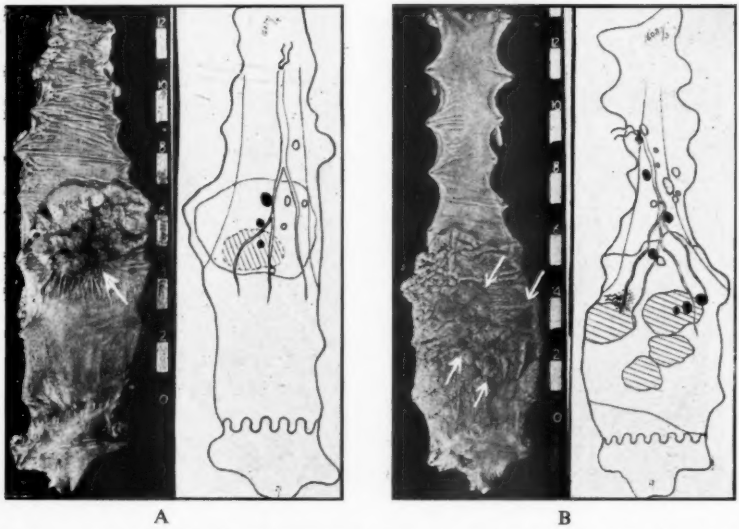


FIG. 3.—Two villous tumours with small areas of adenocarcinoma: both were C cases.



A B

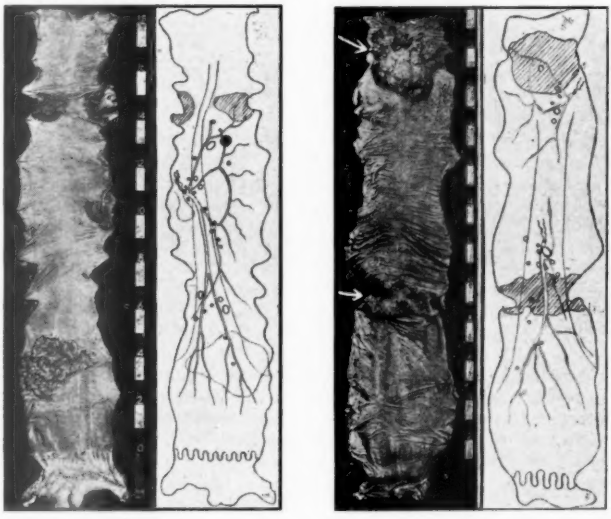
FIG. 4.—Villous tumours with colloid carcinomatous changes, both C cases. The second one had 4 areas of colloid carcinoma and advanced lymphatic spread (C2 case).

own judgment in relation to the history, the clinical findings and the usual known course of these tumours.

Examination under anæsthesia is a preliminary procedure of great value in some cases. When the sphincter ani is relaxed it is possible in many cases to form a much more accurate estimate of the extent of the growth, and to decide if there is any likelihood of it being delivered externally for local resection or whether this is quite out of the question. Further pieces for biopsy can be taken if necessary and the slight delay before finally deciding on the procedure to be adopted is often advantageous.

Treatment.—The tendency to recurrence after local excision of villous tumours of the rectum is well established and I am sure that we all remember cases that illustrate this fact. If small villous tumours of the rectal ampulla tend to recur after local excision how much more should we be diligent in doing a major radical operation for cases of large villous tumours when malignant degeneration is so likely or almost certain! I used to believe that when malignant change supervened on a villous tumour it was likely to be localized and of a low grade of malignancy, but recent experience has convinced me that this is not so, and that a colloid carcinoma or an adenocarcinoma with lymph-node involvement is more common (Figs. 3 and 4).

Other points that favour a radical operation in these cases are the possibilities of multiple tumours, either multiple villous tumours or villous tumours in association with adenomas or actual established carcinomas at a higher or lower level (Fig. 5).



A B

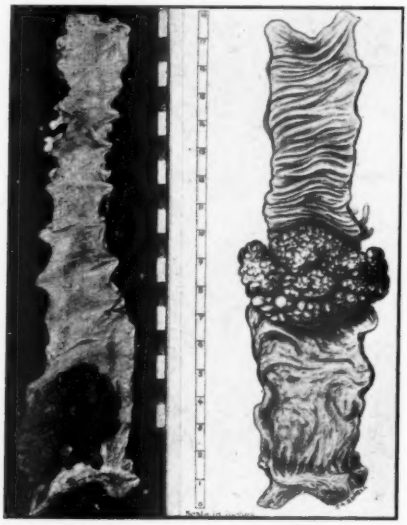
FIG. 5.—Operation specimens showing multiple tumours. In A there was a large villous tumour in the rectal ampulla with a pedunculated adenoma and a carcinoma at a higher level. In B a large villous tumour with colloid malignant change was present in the pelvic colon with an annular carcinoma in the rectosigmoid.

Although a conservative or restorative type of operation might at first sight be considered suitable for a villous tumour which cannot be resected from below, I cannot help feeling that the risk of implantation recurrence must be very great when we consider the innumerable villi on the surface of these broad-based tumours, and the extreme likelihood of some of these villi becoming adherent to the line of suture or actually embedded in the rectal wall during the anastomosis in spite of anti-implantation efforts by irrigation or swabbing with perchloride of mercury lotion.

In addition there is the risk of local recurrence due to the surgeon misjudging the size or precise area of the tumour and in consequence allowing an inadequate margin for the resection. I think we can take it as certain that recurrence will occur if the growth is not completely resected with an adequate margin ($\frac{1}{4}$–$\frac{1}{2}$ in., 6–13 mm.) of normal mucosa all round it, and I should like to put this point to you: if it is difficult or even impossible to determine the exact limits and extent of a villous tumour when we examine it with a finger in the rectum, it is likely to be much more difficult to do this with any certainty or assurance when the growth has to be palpated through the entire thickness of the bowel wall at laparotomy.

Several of the cases of large villous tumours which I have depicted have come right down to the ano-rectal line; in fact in one case (Fig. 6A) I think there is clear evidence of the growth extending down on to the epithelium of the anal canal. For such cases I do not think a pull-through type of operation would be a good proposition.

Results of radical operation.—Out of 11 cases of large benign villous tumours of the rectum treated by perineo-abdominal excision there was one operative death; this occurred in a thin dehydrated patient aged 78 who died on the day after operation from cardiac failure which was probably



A B

FIG. 6.—A, large villous tumour extending on to the epithelium of the anal canal. B, large villous tumour of the recto-sigmoid; the patient survived for 19 years after perineo-abdominal excision.

accelerated by an incompatible blood transfusion. Of the 7 patients operated upon more than five years ago all but one safely reached the five-year mark; this exception was a patient who died over four years after operation from myelomatosis. One patient lived for over nineteen years after operation and died at an advanced age from uræmia and bilateral polycystic kidneys (Fig. 6B); two others survived for fourteen years, and there has been no case of recurrence either in these or in the three more recent cases.

I should like to conclude with the following expressions of opinion:

(1) Large villous tumours of the rectum are usually more extensive than they appear at first sight and pre-operatively it is difficult, if not impossible, to exclude malignant change whether central or peripheral, single or multiple.

(2) Examination under anæsthesia is a preliminary procedure of great value and biopsies can be repeated as indicated. A negative biopsy does not exclude malignant change.

(3) When a large villous tumour occurs in the rectum or recto-sigmoid it is usually best dealt with by a radical combined excision; this operation eliminates the risk of local recurrence and gives an excellent prospect of permanent cure.

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Section of Odontology

President—R. A. Broderick, D.S.O., M.D.S.Birm., F.D.S., M.B., Ch.B.Birm.

[*February* 25, 1952]

SYMPOSIUM ON THE TREATMENT OF ADAMANTINOMA

Professor Robert McWhirter:

Erroneous interpretation of the nature of a pathological process may lead to incorrect treatment. Thus giant-cell tumours of bone were at one time regarded as sarcomata having their origin in the bone-marrow and were actually termed myeloid sarcomata. In consequence of this mistake they were treated by amputation. Now with better knowledge of their true nature thay have come to be treated by more conservative measures and the success obtained clearly justifies the validity of the more modern outlook.

Histology has made valuable contributions to the better understanding of many diseases. So great have these contributions been that at times it has been held that histological evidence alone might provide an adequate basis for the establishment of a classification of diseases. Such an approach to the classification of tumours has been attempted but in many instances has had to be abandoned in the light of the broader more general information obtainable by clinical examination and follow-up studies. Thus hypernephroma is no longer regarded as a distinct tumour of the kidney having its origin in misplaced adrenal cells, and the elaborate classifications applied to brain tumours and to neoplasms of the lymph glands are being replaced by much simpler classifications.

The difficulties which arose in connexion with these attempts were primarily due to too much attention being focused on minor differences in cellular detail and arrangement. It is now recognized that clinically identical tumours may show great variation in their histological structure. All gradations may be found between these variations and occasionally may even be found in a single tumour, thus demonstrating conclusively that the variations do not warrant the application of distinctive clinical terms. By drawing attention to similarities in clinical behaviour the clinician at times may be of considerable assistance to the histologist in the establishment of a satisfactory classification of tumours.

In a large radiotherapy department the clinical experience gained in malignant disease is extensive. It is difficult to fail to note points of similarity between tumours even when they bear names which give no indication of their close relationship. For some time I have been impressed by the very striking resemblance between the clinical behaviour of rodent ulcers and adamantinomata. Thus we may note that both tumours are of slow growth, both are locally malignant and rarely, if ever, spread to lymph glands. Both tend to recur if inadequately treated and, as will be shown presently, both appear to be radiosensitive. While the histological appearances are not always identical, these two tumours nevertheless have many important features in common. Their origin is of particular interest and strongly supports the view that they are essentially of the same nature.

As stated in a previous communication (McWhirter, 1950) both tumours appear to have their origin in those cells of the skin and mucous membrane of the mouth which have either differentiated, or at least possess the ability to differentiate, towards the normal appendages or adnexæ derived from these covering membranes. It is convenient to consider the origin of rodent ulcers in the first place.

The normal cells of the basal layer of the skin may differentiate in either of two directions. Some cells differentiate so as to form a protective surface for the body. These cells become flattened and keratinized so as to form the familiar squames which protect the deeper tissues against bacterial attack and minor trauma. Other cells of the basal layer fulfil quite a different function and extend down into the dermis to form the various appendages of the skin, e.g. the sweat glands and hair follicles. These cells do not undergo squamous differentiation. It is important that they should not do so because, in a sweat gland for example, the gland would very quickly become plugged with a mass of desquamated squames and would be quite unable to function. Two quite distinctive groups of cells are thus derived from the basal layer of the skin.

It is a characteristic feature of neoplastic cells that they tend to differentiate in the direction they would have taken if neoplasia had not occurred. Thus a bone cell when it becomes malignant produces an osteogenic sarcoma, a fibroblast a fibrosarcoma, a glial cell a glioma, &c.

In the basal layer of the skin, therefore, if neoplasia occurs in a cell destined to take part in the squamous protective covering of the body, it would be expected that the cells of this tumour would show some degree of differentiation towards squame formation. This, of course, occurs and in some tumours squame formation is clearly recognizable in the form of the so-called "cell-nests". If, on the other hand, neoplasia occurs in a cell of the basal layer which would normally have given rise to a sweat gland or a hair follicle, or if neoplasia should occur in a cell already in a sweat gland or hair follicle, no such squamous differentiation is to be expected, for, as we have seen, these cells do not normally produce squames.

When fully differentiated, the cells of sweat glands and hair follicles show a lesser degree of morphological change from the cells of the basal layer than do the cells which undergo squamous differentiation. The cells of tumours derived from a sweat gland will, therefore, show less morphological change from the basal layer of the skin and it is this feature which has led to this group of tumours being called basal-cell carcinomata. It will be recognized from what has already been said that the term is unfortunate because both squamous epitheliomata and "basal-cell carcinomata" are ultimately derived from the basal layer of the skin.

In the older teaching it was thought that well-differentiated squamous epitheliomata arose from those cells of the skin which had already undergone a considerable degree of differentiation towards squame formation. The less well-differentiated squamous epitheliomata were thought to arise from cells nearer the basal layer. It is clear this view is quite untenable because by this reasoning the nearer the origin of a squamous epithelioma to the basal layer of the skin the more markedly does the tumour differ from the so-called basal-cell carcinoma. Undifferentiated squamous epitheliomata show a high tendency to metastasize to lymph glands. Basal-cell carcinomata do not show this tendency. Undifferentiated squamous epitheliomata grow rapidly. Basal-cell carcinomata grow slowly.

The alternative name for basal-cell carcinoma is, of course, rodent ulcer. This term is equally unfortunate because many rodent ulcers, especially in their earlier stages, are not ulcerated. The term "rodent ulcer" has been in use for so long that it is difficult to replace it and it certainly would be unfortunate to replace it by the term "basal-cell carcinoma" which perpetuates the confused ideas regarding the origin of this tumour and squamous epithelioma. Foot (1947) suggested the term adnexal tumour for the rodent ulcer group and this would appear to be very appropriate because it does denote the true origin of these tumours.

Fig. 1 shows a primordial hair follicle in a 13 cm. human fœtus and the striking resemblance which it bears to a rodent ulcer (Fig. 2) should be noted.

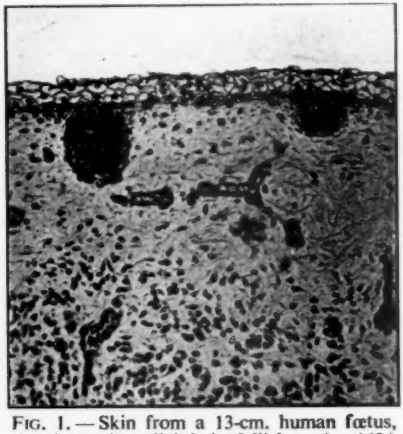

FIG. 1.—Skin from a 13-cm. human fœtus, showing primordial hair follicles. (× 160.)

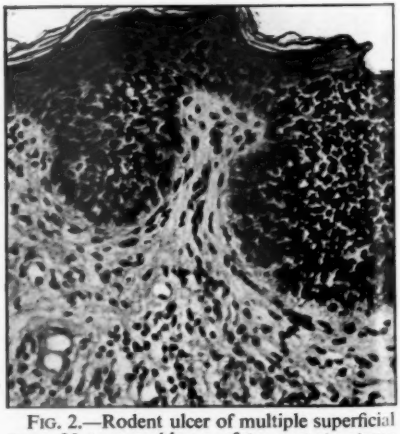

FIG. 2.—Rodent ulcer of multiple superficial type. Note resemblance of tumour structures to primordial hair follicles. (× 160.)

Occasionally the cells of a rodent ulcer show such a degree of differentiation that it is possible to recognize attempts at hair-follicle formation or sweat gland formation. This finding further strengthens the view that rodent ulcers are derived from sweat glands or hair follicles or at least from cells which are destined to differentiate in this direction (Figs. 3 and 4).

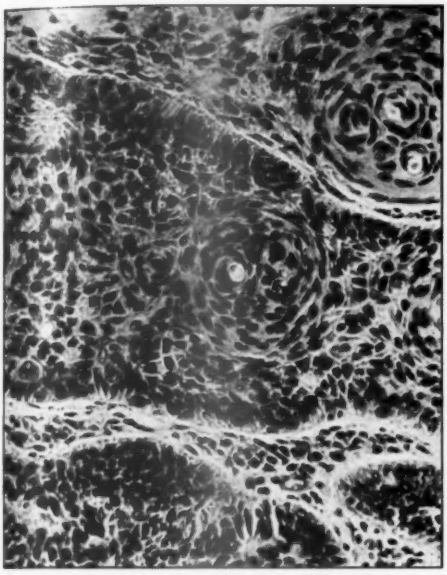

FIG. 3. — Rodent ulcer showing differentiation to hair shafts and sweat ducts. (× 180.)

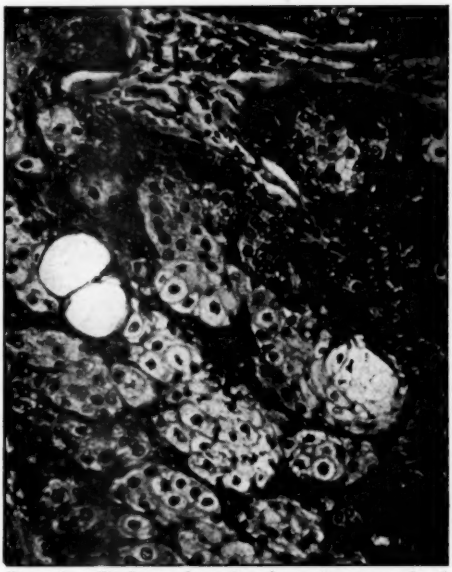

FIG. 4. — Rodent ulcer showing sebaceous gland differentiation. (× 180.)

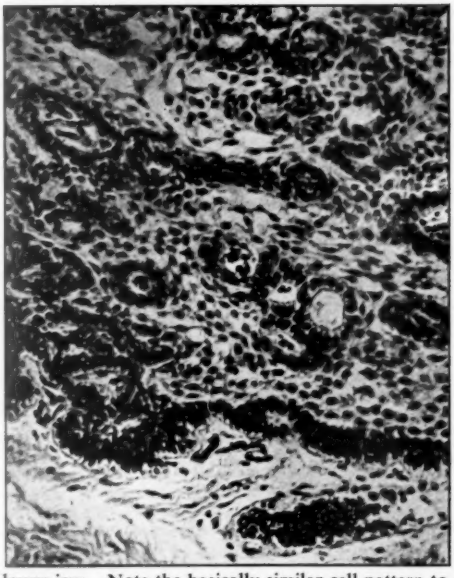

FIG. 5.—Adamantinoma of lower jaw. Note the basically similar cell pattern to that found in rodent ulcers and the development of the characteristic reticulate epithelium in the centre of the tumour masses. (× 180.)

It is of interest to note that some adnexal tumours are wholly subcutaneous and these are presumably derived from deeply penetrating sweat glands or hair follicles. On the antero-medial aspect of the leg and over the acromion process where bone lies immediately deep to the skin, some of those deeply placed tumours may actually involve the bone. The histological appearances of these tumours in bone have sometimes led to their being termed adamantinomata and the occurrence of adamantinomata in the tibia and acromion process has always been puzzling. The view just expressed gives a simple explanation of their origin. They could equally well be called basal-celled carcinomata. The fact that they have been termed adamantinomata is of great interest because adamantinomata also arise from adnexal structures.

The lining membrane of the mouth is, of course, squamous epithelium which shows no significant difference in its histological features from the skin. There is a basal layer and the cells of the basal layer either differentiate towards squame formation or towards the structures derived from the mucous membrane—in this case the teeth. The teeth develop as a downgrowth of cells of the basal layer into the mesenchyme of the future alveolar margin. The cells of the dental lamina do not show squame formation and undergo only a minor degree of morphological change from the cells of the basal layer. The tumours derived from these cells are called adamantinomata and as might be expected their histological features are similar to those of rodent ulcers. In adamantinomata as in rodent ulcers the margins of the tumour are well defined from the surrounding tissues by a basal layer of cuboidal cells. The centrally placed cells, often referred to as the reticulate epithelium, closely resemble one another (Fig. 5). As in rodent ulcers this finding might easily convey the impression that the tumour was undifferentiated and therefore rapidly growing, a feature which does not fit with the known clinical facts. The cells are, in fact, differentiated but the differentiation occurs without gross morphological change. Where some differentiation occurs the histological picture may be slightly modified but the tumour still remains an adamantinoma.

Most of the adamantinomata, of course, lie within the bone of the jaw but occasionally the tumour may arise directly from cells of the basal layer of the mucous membrane and the tumour is then superficially placed. These superficially placed tumours are sometimes referred to as superficial adamantinoma but as a general rule are called basal-cell carcinomata. From what has been said it would appear to matter little which term is applied.

It was for a long time believed that adamantinomata rarely occurred in the upper jaw but it is now recognized that some antral tumours are, in fact, adamantinomata. This is easily explained for, as would be expected, adamantinomata arising in the upper jaw naturally tend to extend in the direction of least resistance which is into the antra. Such tumours may be reported as "entirely undifferentiated tumours", or as "carcinomata of basal-cell type". The slow growth and the absence of spread to lymph glands often enables the clinician to recognize their true nature. (It should, of course, be noted that the majority of tumours of the antrum are squamous epitheliomata.)

The last point I wish to refer to is the occurrence of adamantinomata at the base of the skull. The presence of adamantinomata in the region of the sphenoidal air sinus or in relationship to the pituitary fossa has always been difficult to understand. It will be recalled that the anterior lobe of the pituitary is derived from the lining membrane of the primitive oral cavity. The anterior lobe of the pituitary is, therefore, an adnexal structure. The path taken by the cells is later occupied by the sphenoidal sinus. Some cells may persist along this track and should those cells undergo malignant change they possess, as would be expected, the histological structure of the other adnexal tumours to which I have just referred. Like rodent ulcers and the adamantinomata of the jaws these tumours are slow growing and they do not tend to metastasize to lymph glands.

If the views just expressed are accepted they bring together a group of tumours which hitherto have been regarded as distinct and separate. Their acceptance also gets rid of the confusion which surrounds the so-called adamantinomata of the tibia and of the base of the skull.

Treatment.—Still more important is the bearing of these views on the treatment of adamantinomata. While in some centres adamantinomata are recognized as truly malignant tumours and are radically treated, too often the treatment applied is totally inadequate for their eradication. Thus, commonly adamantinomata are treated by simple curettage. Recurrence under these circumstances is inevitable. If adamantinomata are accepted as being similar in nature to rodent ulcers these inadequate methods of treatment may be abandoned for it is well recognized that rodent ulcers, whether they involve bone or not, cannot be cured by simple curettage. The more radical form of treatment of adamantinomata is resection of the affected portion of the bone, taking care to remove a margin of apparently healthy bone so as to reduce the risk of recurrence.

We encountered a number of these tumours which had been operated on previously but where the operations had been inadequate and the tumour had recurred. So extensive was the recurrence in some cases that a very wide resection of the jaw would have been required. When the tumour is so large as to require removal of the whole width of the jaw, the defect must be repaired by the insertion of a so-called bone graft. Such "grafts" may be successful but this is not always the case and the

resulting deformity may be considerable. It is not always appreciated that these pieces of bone inserted are not, in fact, grafts. Transplantation of a large piece of bone results in the death of the bone and the so-called graft acts merely as a spacing device which, in due course, becomes surrounded by new bone. In a satisfactory case the "graft" is ultimately absorbed.

Because of these difficulties and because of the apparent identity of adamantinomata and rodent ulcers, we have attempted treatment of a number of cases by means of X-ray therapy. The number of adamantinomata so far treated is too small for any dogmatic statement to be made and it is certainly too soon to state that this will prove to be a reliable method of treatment. It would appear that it can be successful in some cases. With further experience and improved technique, radiotherapy may become an alternative method of treatment to resection.

(Radiographs and clinical photographs were presented to show the results obtained by radiotherapy.)

I am indebted to the Editor of the *Journal of the Faculty of Radiologists* for permission to publish the photomicrographs (Figs. 1–5).

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Mr. G. M. Fitzgibbon:

The typical adamantinoma is a tumour of epithelial origin, showing masses of well-defined basal-type cells very similar to those of the enamel organ, a central area of stellate reticulum, which is often degenerate, and shows merely as a cystic space.

A commonly accepted source of origin of these tumours is from some remnant of the epithelium of the primitive tooth germ. The resemblance of some adamantinomatous tumours to rodent ulcers has been commented upon many times by different authors. There are, however, two ways in which these tumours are noticeably different from the common rodent; one is the presence of the characteristic stellate reticulum, and the other is that it is usual for an adamantinoma to remain confined within the periosteum. It is rare to see adamantinoma outside the bone, unless operative trauma or a pathological fracture has occurred.

The majority of these tumours occur in the lower jaw, and nearly always in the angle region. Clinically they show enlargement and expansion of the mandible, which may show externally or internally. It is often possible to feel and appreciate the cystic nature of the tumour and unless a pathological fracture has occurred, they seldom cause pain. The clinical differences between one of these tumours and a simple dental cyst are so small and inconstant as to make it impossible to be certain on clinical grounds of their exact nature.

The X-ray appearances are often confusing. The usual appearance of an adamantinoma is a multilocular cystic lesion in the angle region of the mandible, often extending up the ascending ramus. There is considerable thinning and expansion of the cortical bone. The tumours may arise at any age, and when first seen are usually found to have been present a number of years. I have operated on, or have personal knowledge of, some 15 cases. Their average age when they came into my hands was 49 years, and in one instance the tumour was known to have been present for fifty years. The average length of history of these cases was thirteen years. These tumours are not common, and few long series of cases have been reported. The one constant feature for all communications on the subject is the high recurrence rate of these tumours. This is a most unfavourable comment on the efficiency of the treatment, and it should be possible in dealing with a tumour of such low malignancy to obtain far better results. One factor which no doubt contributes to the high recurrence rate is the difficulty of exact diagnosis.

The histological features of these tumours are often different, partly because the appearances vary in different parts of the same tumour, and partly because there is a good deal of confusion of thought as to what may be accepted accurately as an adamantinoma. I think it is not justifiable to classify a case as an adamantinoma unless the characteristic basal-cell epithelium is present and there is some evidence of stellate reticulum formation. Tumours are frequently reported on as adamantinomata which are epithelial tumours, more approximating to epithelioma. It must be remembered that every type of epithelial tumour from a simple cyst to a highly malignant anaplastic epithelioma may be found in the mandible.

The treatment of these tumours should be excision. It is a bad practice to use a curette on an ordinary rodent ulcer, and it is just as bad to attempt to use a spoon in these cavities in the jaw. The area should be excised with a zone of normal bone around. In an extensive involvement of the mandible it may be necessary to remove half the mandible from the symphysis to the temporomandibular joint, and very little deformity results from this procedure. The function of a half lower jaw is often excellent, and most of these patients manage to control the swing extremely well, and some of them even manage to wear and use a denture.

With regard to the treatment of adamantinoma by radiation, such experience as I have had has been unsatisfactory. In 2 cases of which I have personal knowledge, the tumours have retrogressed to a point, but are still obviously present. One aspect of radiological treatment which one always has in mind is the way in which previous radiation adds so enormously to operative difficulties, and healing is impaired. There are other possible dangers, such as damage to the skin and superficial tissues, and sometimes damage to the bone underlying them, resulting in radionecrosis, infection and severe pain. Surgery is, I am sure, the right treatment at the present time. It is sheer chance in so many cases which portion of the tumour one sends to the pathologist, and so often it is not possible to make an exact diagnosis, that excision is in most instances the quickest, safest and most satisfactory answer to the problem.

(A short film was then shown giving the details of removal of a half mandible.)

Dr. W. Shanks:

13 cases of adamantinoma have been treated since 1943, with a combination of simple surgery and irradiation.

Of the 13 cases, 4 were male and 9 female, or if 1 doubtful male case be excluded—a case of basal-cell carcinoma of mandible—the ratio of female to male was 3 to 1. The youngest was aged 21 years and the oldest 79 years.

The length of history varied from a few months to twenty years, and the cases were distributed as follows, at the time the tumour was first observed.

None in the first decade; none in the second decade; 5, all female, in the third decade; 1 in the fourth decade; 3 in the fifth decade; 2 in the sixth decade; 1 in the seventh decade; 1, a doubtful case, in the eighth decade.

The main incidence would appear, therefore, to be with young adults between 20 and 30 years, as almost half fell into this category.

Summary of results.—10 cases were treated by simple surgery and radiotherapy.

Of the remaining 3 cases, 1 required irradiation for a recurrence following radical surgery and bone graft, 1 has had presumably radical surgery two years after conservative surgery without irradiation, 1, aged 79—basal-cell carcinoma—has developed a cerebral hæmorrhage.

The treatment fell into two main groups:

	Surgery + combination of X and gamma rays	Surgery + X-rays
Total number of cases in group	5	5
Free from recurrence up to eight years	3	3
	2 cases required excision and bone graft: 1 for sequestration, and 1 for recurrence	2 cases required excision: 1 for sequestration and 1 for residual tumour

There has been no mortality in the series. 11 are free from disease; 1 awaits an operation; and 1, aged 79, has had a cerebral hæmorrhage.

Mr. B. W. Fickling:

In assessing the results of treatment of adamantinoma a long-term follow-up is essential, for the tumour is slow growing and it is well known that second operations are commonly not required for four to ten years. Radiotherapy may well prolong this interval without being curative. This is the basis of the conservative approach which has so long been in vogue. Textbooks still advise enucleation and curettage as the treatment of choice, with or without electrocautery or coagulants, and reserve jaw resection for large tumours with several recurrences (Stones, 1951; Romanis and Mitchiner, 1948). A survey of the literature indicates that enucleation and partial resection even in the best hands lead to recurrence, and few would accuse an earlier generation of surgeons of being perfunctory in their approach to neoplasms. Mead (1946) quotes Quick "Surgery to be effective requires resection and this is disfiguring". At the St. Albans Plastic and Jaw Unit simple adamantinoma has only been encountered in the mandible and limited resection and conservative operation are regarded as having failed. Advances in plastic surgery have to a very large extent eliminated the criticism of disfigurement. The treatment of choice is therefore radical resection by an external approach, function and contour being restored by bone graft and prosthesis. Such treatment is not so applicable to the maxilla. Only one case has been treated in the upper jaw. It proved on section to be malignant adamantinoma, appeared to arise from Rathke's pouch, and caused orbital symptoms prior to death in ten months.

Of 11 cases treated in the Unit only 1 had received radiotherapy, the course extending over seven years. There had been operations at age 36 and 37 followed by radiotherapy which was discontinued when obviously not controlling further growth. A very large tumour was resected at age 49 and a bone graft inserted four months later. Changes in the soft tissues induced by radiotherapy militated against a good cosmetic result. 1 case had had three previous operations, another had two, while 3 cases had one earlier operation. In some cases the description indicated that the operation was for a cyst although details are lacking. 5 cases had had no previous operation.

Analysis of the cases treated reveals the following points and indicates a plan of treatment.

Diagnosis.—There is too much disparity in the radiographic appearances to make this a safe method of diagnosis. Not all cases show the honeycomb sponge appearance, while large simple cysts often appear to show multiple cystic spaces due to septa in the bony walls acting as strengthening ribs and struts.

Biopsy is required and an adequate specimen should be obtained. Since excision is likely to follow, a mouth approach leaves problems of closure. The possible origin of the tumour leads one to suspect the alveolar mucosa, while in many cases teeth in the area require to be extracted. In most cases therefore the mouth approach is used, adherent mucosa excised and the flaps carefully approximated as after alveolectomy.

Determination of limits.—By careful radiography including dental and occlusal films. Approximately ½ in. of normal bone should be excised with the tumour.

Extraction of marginal teeth at least three weeks before resection with closure of mucoperiosteum to permit healing. This is not essential, but if it is done at the time of resection a mucosal defect occurs at the neck of the last standing tooth which defies closure and leads to infection.

Fitting of splints.—When teeth are present dental cap splints are fitted with screw locking plates in normal occlusion (Fickling, 1946). Attachments for pin fixation are required whenever an edentulous posterior fragment will be left. Provision for flanges may be made in those cases in which the condyle will be excised.

Excision.—By external approach. The mouth was opened at some point in each case and was closed with mattress sutures. Instead of drainage a spigoted rubber tube is employed through which 1–3 ml. of penicillin solution 5,000 units per ml. is passed for three to five post-operative days. Some degree of infection has supervened in half the cases due to the mouth involvement and the considerable dead space left.

Interval.—In view of the above points only one immediate bone graft has been inserted. On account of radiotherapy one bone graft was delayed four months. The interval in the remaining cases averaged four and a half weeks.

Bone graft.—A combination of cancellous rods and chips from the iliac crest is employed. In 4 cases the condyle had been excised and immobilization was maintained for ten to twelve weeks, in the other cases four to six weeks sufficed.

Prosthesis.—No attempt should be made to insert dentures at an early date owing to moulding. Epithelial inlays are seldom required either to create a sulcus or to restore contour.

Relevant problems in the treatment of dental cysts.—Certain authorities argue that the lining of all cysts of the jaws should be removed at operation because certain adamantinomata appear to develop after inadequate treatment of cysts. The complications of removing all cyst linings are not inconsiderable, while it can be contested whether enucleation of a potential adamantinoma would prove effective. It is more reasonable, therefore, to treat each cyst on its merits, removing or leaving the lining as indicated by the factors in each case, and to submit a portion of each cyst wall and all suspicious areas to histological examination.

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Adamantinoma, Primitive Type, Treated both Surgically and with Radiotherapy.—GEORGE T. HANKEY, O.B.E., T.D., F.D.S., M.R.C.S.

Mr. G. W. C., aged 64, a farmer; of good general health except for an osteoarthritic hip-joint.

History.—1942 (nine years earlier): Patient first noticed the left side of his face was swollen. There was no pain or disability. Three years later (29.3.45), when the swelling had reached the size of a pigeon's egg, he sought medical advice because of pain on eating.

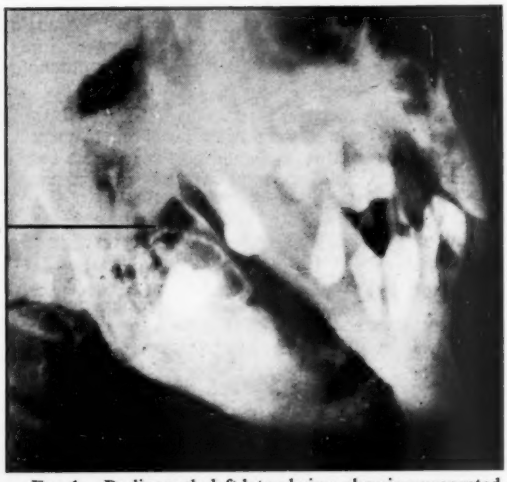

FIG. 1.—Radiograph, left lateral view, showing unerupted |8 with roots embedded in dense sclerotic bone and crown covered by an area of rarefaction limited by a thin, sharply outlined bony shell (A). The ramus behind is coarsely honeycombed.

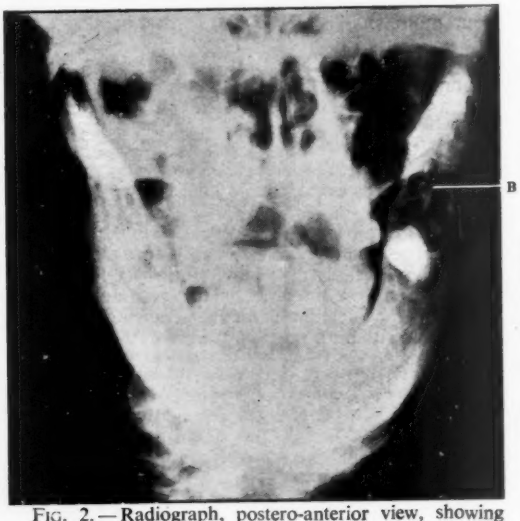

FIG. 2.—Radiograph, postero-anterior view, showing rarefaction and honeycomb appearance (B) of left angle and ramus.

First operation (25.4.45).—The surgeon at his local country hospital diagnosed a parotid tumour and approached the swelling by an external incision behind the left ramus. When opened, the swelling proved to be a large cyst of the mandible expanding both inner and outer plates. A small portion of the tumour was removed for biopsy and the wound closed; the biopsy was inconclusive. There is no record of an X-ray film.

Second operation (10.5.45).—The same surgeon approached the cyst both intra- and extra-orally. The contents were removed by curettage and the bony walls were crushed in. The cavity was plugged.

The histological report on a portion of the material removed was: "A fragment of buccal mucosa deep to which is a cyst lined with poorly developed basal and prickle-celled epithelium. Adjacent are a few scattered groups of undifferentiated epithelial cells probably paradental epithelial debris." (I have been privileged to see a slide from the same block; the appearance was that of a dental cyst.)

20.9.45: *Referred to a radiotherapeutist* at a London hospital. There is no record there of a further biopsy, of diagnostic X-rays, or of a dental consultant's opinion. The left side of the mandible was irradiated with 2,250 r in three treatments spread over three weeks. A month later a previously persistent discharge from the wound had ceased. The patient remained well until last seen by the radiotherapeutist on 4.7.50. The radiotherapy had apparently cured or confined the condition.

21.9.51: *On examination* at St. Bartholomew's Hospital (six years after surgery and radiotherapy and nine years since the earliest sign): The mouth had sixteen very septic teeth standing. There was a hard bony fullness of the left angle and ascending ramus of the mandible, expanding both inner and outer plates. [illegible] were old incision scars externa[illegible] moved freely over the swelling. [illegible]e mucous membrane of the mouth was normal colour; there was no sinus. There were no symptoms.

X-ray films (Figs. 1 and 2) disclosed an unerupted lower third molar, crown uppermost, its roots embedded in dense sclerotic bone; the sharp bony outline of what

might have originally been a follicular cyst covered the crown; and behind almost all the ramus was honeycombed with small rarefied areas separated by unusually sclerotic bone. (Until now the connexion of the unerupted wisdom with the cyst had either been overlooked or disregarded.)

5.10.51: *Third operation* by myself under a general anæsthetic. All the septic teeth were first extracted. On removing the bone covering the cyst, the space beneath was occupied by a tough, pinkish, fibrous material; this was shelled out and then the wisdom excised. The loculi in the ramus were broken down and the rest of the tumour removed by curettage as thoroughly as possible. The purpose was to determine the pathology of the tumour and the effect of the radiotherapy upon it. (Hemi-excision of the jaw had to be postponed at this time because an arthrodesis for his ankylosed hip had priority.) The wound healed quickly without complication.

Histological report.—Naked eye the material was described as: "friable brownish tissue with fibrous tissue stroma." Microscopically it was: "An adamantinoma infiltrating in very dense scar tissue. A good deal of secondary calcification of the scar tissue with abundant hæmosiderin and cholesterol deposits. There are a small number of irregular epithelial areas the cells of which are columnar or spinous in type and the central cells show a tendency to separation by œdema fluid" (Figs. 3 and 4).

FIG. 3. — Photomicrograph (× 160). Stained hæmatoxylin and eosin. Strands of undifferentiated epithelium in a very dense acellular fibrous stroma.

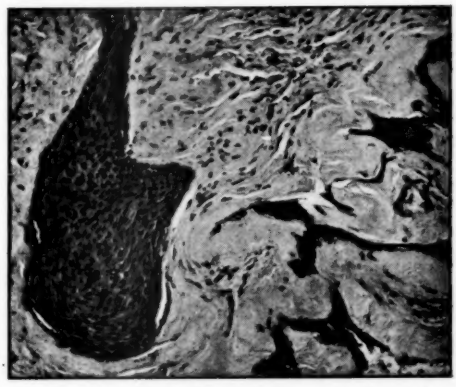

FIG. 4. — Photomicrograph (× 140). Stained hæmatoxylin and eosin. Another field, showing a larger mass of epithelial cells with slight intercellular œdema. Here the stroma is more cellular.

CONCLUSION

How much of the histology is the result of previous surgery followed by radiotherapy is hard to say; the fibrous tissue was very tough and not apparently neoplastic, and the bone was very sclerotic—both probable effects of the radiotherapy. The tumour is a solid type of adamantinoma composed mostly of fibrous stroma in which are included strands of undifferentiated epithelial cells resembling remnants of the dental lamina. Thoma (1950) would probably classify it as the primitive type of adamantinoma; had the fibrous stroma shown a neoplastic tendency, both he and Lucas (Lucas and Thackray, 1951) would term it an amelo-blasto-fibroma. Cholesterol deposits in an adamantinoma, as seen in other parts of this section, seem to be rare. The tumour was still active.

I am indebted to Dr. R. J. R. Cureton of St. Bartholomew's Hospital for the pathology and preparation of the photomicrographs, to Professor A. E. W. Miles of the London Hospital for his advice, and to my house-surgeon, Mr. P. H. S. Hooper, for his assistance in gathering the history.

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Section of Dermatology

President—G. B. DOWLING, M.D., F.R.C.P.

[*May* 15, 1952]

Acute Disseminated Lupus Erythematosus (Now Quiescent on ACTH).—DENIS ELLIOTT SHARVILL, M.R.C.P. (for SYDNEY THOMSON, M.D.).

Miss M. L., aged 22. Secretary.

Admitted to King's College Hospital Unit, Dulwich Hospital, 24.4.52, complaining of rash on face, hands and legs and of inability to eat or drink.

History of present illness.—Was perfectly well until the end of March (a week-end of snow) when she felt cold and sat by the fire. This brought on redness of the legs and fingers, which she considered to be chilblains. She applied elastoplast to the fingers, and when she removed it they were raw and bleeding. Ten days later she felt giddy and lethargic and spent a week in bed; her doctor diagnosed chilblains and food poisoning and gave five injections of penicillin. A week before admission the rash appeared on the face and got rapidly worse. The fingers also rapidly deteriorated with profuse bleeding, and she noticed pain and swelling of the right knee. Her mouth became very sore so that she could neither eat nor drink, although she felt hungry. She had a slightly sore throat. She felt quite well in herself. She has not taken sulphonamides or any other drugs.

Previous history.—No major illnesses. No rheumatism. 1947: Chest X-ray normal. 1948: Measles. 1951: Went hiking and got sunburned. The skin took three months to become normal, but she attaches no significance to this.

Family history.—Nothing of note.

On examination.—A symmetrical erythematous rash involved the face, forehead, ears, shoulders, upper arms, backs of hands, fingers, shins and toes. It was of a vivid purple red colour, most marked on the face and fingers and very sharply demarcated.

On the face the batswing area was strikingly involved. There was no scaling or plugging. In the mouth the palate showed erythematous lesions, and hæmorrhagic crusts were present on the lips.

All the fingers were severely involved, the extensor surfaces more than the flexor, distally more than proximally. At the nail folds and over the interphalangeal joints there was erosion of the epidermis and profuse bleeding.

A few purpuric macules were present on the trunk. The shins showed sheeted erythema. The toes showed changes similar to the fingers, but of lesser degree.

On general examination.—She was alert and co-operative, but looked desperately ill. The temperature and pulse-rate were raised. The tongue was very dry. During the previous week the temperature had varied between 100° and 102° F.

No abnormality was found in the cardiovascular system except for a soft systolic murmur at the apex. Blood presure 120/45. The respiratory system appeared normal. The spleen and liver were not felt. There was no lymph gland enlargement.

26.4.52 (Dr. Samuel Oram): There is no real evidence of cardiac involvement on clinical grounds . . . the soft systolic murmur could be accounted for by fever and tachycardia.

9.5.52 (Mr. R. P. Crick): When first seen on 29.4.52 a few patches of white exudate were visible ophthalmoscopically lying superficially in the retina, close to and some overlapping the larger branches of the retinal vessels near the optic disc. Though circumscribed their appearance suggested that they were of recent origin. No other fundus abnormalities were seen and the visual acuity was unimpaired. To-day only one patch of exudate remains in the left eye.

Special investigations on admission.—Urine: Heavy cloud of albumin. Scanty leucocytes and red cells. Numerous hyaline, cellular and granular casts. Sterile after eighteen hours' culture.

Blood (25.4.52): R.B.C. 3,500,000; Hb 11·3 grammes%. Hæmatocrit 32 mm./100 mm. Leucocytes 2,100/c.mm. Platelets were present in adequate numbers on this date. Blood film: Neutros. 58, lymphos. 39, monos. 3%. Corrected E.S.R. (Wintrobe) 26 mm./hr. E.S.R. (Westergren) 80 mm./hr.

L.E. cells were produced on adding the patient's plasma to her own leucocytes and to normal bone-marrow.

Bone-marrow was not examined initially as the patient was in such discomfort, and since it was thought that it might be dangerous in view of the low white count and bleeding tendency. (On 12.5.52 bone-marrow appeared essentially normal.)

Skin biopsy was not carried out. Serum proteins (suspect for technical reasons): Total 5·38 grammes/100 ml. Albumin 3·41 grammes/100 ml. Globulin 1·97 gramme/100 ml. (Chromatography showed reduced albumin and increased α 2 globulin.) Blood urea: 40 mg./100 ml. Throat swabs: No hæmolytic streptococci. Twenty-four-hour urine showed no abnormal porphyrins. 17-ketosteroids normal.

Chest X-ray normal. Serum proteins repeated 15.5.52. Total 5·68 grammes/100 ml. Albumin 3·08 grammes/100 ml. Globulin 2·60 grammes/100 ml. A.G. ratio 1·18 : 1.

Coombs' test negative.

Treatment and progress.—The hands were kept constantly soaked in wet dressings of hydrarg. perchlor. 1 : 2,000 in normal saline which gave great relief; sepsis did not appear.

ACTH 40 mg. eight-hourly was started on 26.4.52. By 27.4.52 she felt vastly better, could eat and drink without discomfort, and the temperature had fallen to normal.

By 28.4.52 the erythema was visibly fading. W.B.C. 3,300. The hands were no longer bleeding. On 29.4.52 ACTH was reduced to 80 mg. daily. On 2.5.52 the face was very much paler and beginning to scale. The hands were painless. She talked of getting up and going home.

3.5.52: ACTH 60 mg. daily.

7.5.52: ACTH 40 mg. daily.

On 8.5.52 the temperature rose. A painless subcuticular whitlow appeared and was evacuated. ACTH raised to 60 mg. daily on 9.5.52.

13.5.52: Temperature settled. Still well.

Comment.—The patient's serum proteins in the first instance were normal, but the result was suspect. Clinically, the cardiologist said there was no evidence of cardiac involvement, but in the electrocardiogram changes in the T waves were definite and indicated involvement of the myocardium. The clinical response to treatment was dramatic; there was subjective improvement within eight or ten hours of the first injection of ACTH and objective change in the erythema within twenty-four hours. I do not know what mepacrine does in acute disseminated lupus erythematosus. The sedimentation rate has remained very high. The white count has gone up from 2,000, when she started, to 3,200 in ten days, and 4,000 to-day.

Dr. W. M. Davidson: I investigated this case hæmatologically: lupus erythematosus cells were easily demonstrated, using the peripheral blood. Otherwise, apart from the leucopenia, thrombocytopenia and slight anæmia, there was nothing important found in the blood or bone-marrow.

The President: Is the Hargraves' cell quite easily discoverable?

Dr. Davidson: When the cases are definite they are relatively easy to discover. Recently in another undoubted case it was simple to show the cells during an acute phase. The only important point appears to be to give live leucocytes a certain amount of time in contact with the patient's plasma *in vitro* to perform the act either by absorption or some other change.

Dr. F. Ray Bettley: It has been asked whether mepacrine has any effect in the acute case. The only such case I have treated with mepacrine was a woman who had all the objective signs of acute lupus erythematosus without a great deal of systemic disturbance. She responded at once: she relapsed when we ceased to give the drug, and there was a further response on re-starting. Both responses and relapses occurred within about twenty-four hours. The dose was 100 mg. a day.

Dr. L. Forman: A case in Guy's Hospital of subacute disseminated lupus erythematosus with a slight temperature has responded very satisfactorily to mepacrine. The erythema has faded and she has put on weight. Hargraves' cells present in large number in bone-marrow have now become difficult to demonstrate. Dr. R. Waterfield has watched the formation of the Hargraves' cell under the phase-contrast microscope. He saw the polymorphonuclear cells advance on the bodies and surround them, the protoplasm of the phagocytic cell flowing round the lupus erythematous body. However this attachment may not be permanent. After a time, from a few minutes to two hours, the leucocytes may slip off again. Thus a fixed and stained smear might not reveal the lupus erythematous cells.

I should like to ask Dr. Sharvill if he considers that the dissemination of his case of lupus erythematosus might have been caused by the pencillin. I have recently seen a post-mortem on a fatal case where streptomycin given over a period of a month was followed by dissemination of this disease. One knows that patients with lupus erythematosus do sensitize readily to antibiotics.

Dr. J. Sommerville: A colleague of mine in Glasgow has told me that he has treated a very acute lupus erythematosus with mepacrine with dramatic results on the skin and on the general manifestations. We had a case in which cortisone treatment was carried on for three weeks, and no further treatment was necessary.

Dr. H. R. Vickers: I would like to raise a note of warning in this case. My colleague, Dr. I. B. Sneddon of Sheffield, had under his care a case similar to this. She responded dramatically to ACTH and was to have been demonstrated at the January meeting. Her sedimentation rate remained raised and a few days before she was to be demonstrated she relapsed. She rapidly went downhill and died within about ten days of the relapse in spite of ACTH and cortisone in large doses given intravenously. I think in this patient, since the sedimentation rate is still very high, the chances are that she will relapse and probably die. The case I have mentioned is being prepared for publication by Dr. R. H. Marten, the Registrar in the Department.

Dr. C. H. Whittle: In a case shown by us here, December 1951 (*Brit. J. Derm.*, 1952, **64**, 295), there has been a nine-months remission following a short course of ACTH. But there has been a persistent polymorph leucopenia which we regard as an indication of possible further relapse, and recently some return of lesions on the fingers indeed suggests relapse. The question whether to continue the ACTH or not is often settled by the limited amount available. We are considering giving mepacrine.

Dr. I. R. Marre: It is possible surely that under ACTH some other infection is supervening, particularly tuberculosis. I wonder whether an investigation of the lungs should not be undertaken. Another point of interest is that I am now trying my second case of disseminated lupus erythematosus with calcium aspirin. Both the first and second cases are doing very well. This substance has presumably a cortisone-like action.

Dr. W. G. Tillman: I had a case of lupus erythematosus which was under my care for some years. The patient never had ACTH. Recently she died after an operation for relief of small intestinal obstruction. On histological examination the obstructing part of the ileum turned out to be affected by periarteritis nodosa.

Dr. G. A. Hodgson: I should like to ask whether paludrine has the same effect as mepacrine. We have treated several cases of disseminated lupus erythematosus with cortisone and ACTH, and the sedimentation rate does not appear to bear any relation whatsoever to the effect of the drug. One case of disseminated discoid lupus erythematosus, almost moribund, was put on cortisone and then on gradually decreasing doses of ACTH for some two months and recovered. She maintained a fairly steady state for six months, but then started to relapse. When she first came in the sedimentation rate was about 20 mm. in the first hour (Westergren), and as soon as she had cortisone it went up to about 50 mm. and remained up all the time.

Dr. W. J. O'Donovan: It was taught and accepted when I was first studying dermatology that at the post-mortem on cases of acute disseminated lupus erythematosus nothing characteristic and explanatory of the disease or death was discovered. No hæmolytic straining of the aorta, no endocarditis, no swollen spleen, only rather marked swelling of the greater organs. Such was my own experience.

Linking with the grave prognosis I have been accustomed to associate always an instability of the personal relationships of the patient. Lupus erythematosis itself can be at times a very varying condition.

I am grateful that this case has been shown to-day. I have recently had under my care a very similar case that was very profoundly ill. Whilst in Hospital the patient was at times very withdrawn from this world and I have seen her several times since her discharge and her mental state is characterized by a great timidity, a fixed desire to return to a handicraft of which she is now incapable and an inability to take in notions quickly. The presence of this mental state is very suggestive that danger is not past.

The President: It appears from the American literature that those with considerable experience of cortisone in the treatment of systemic lupus erythematosus, find that it does not alter matters greatly in the long run. The dramatic clinical response is not accompanied by a fall in the raised sedimentation rate and the Hargraves' cell is said not to disappear. Renal involvement appears to be of serious prognostic significance.

Dr. W. M. Davidson: Although this patient has not yet developed any unusual antibodies, abnormal antibody formation appears to be quite a well-known phenomenon in lupus erythematosus. In one of our cases anti-blood group S antibody developed and it is interesting that several of the other cases in which this rare antibody has been found had lupus erythematosus. This tendency to antibody formation seems to be a very important feature and should be remembered when contemplating a blood transfusion.

Dr. Sharvill, in reply: There is no evidence of tuberculosis. The chest X-ray is normal, and no acid-fast bacilli have been found in the sputum or urine.

I hope later to be able to try the effect of mepacrine, when the condition is more stable, or perhaps that of oral cortisone. I do not know whether paludrine has any effect: I see no reason why it should—it is not chemically related to mepacrine.

I do not think that dissemination was caused by penicillin; systemic illness was present before it was given.

When we reduced the dose of ACTH to 40 mg. a day her temperature rose, settling on a subsequently increased dose. This may, however, have been due to the presence of a subcuticular whitlow.

Addenda: 18.7.52.—Seven weeks ago ACTH was reduced to 30 mg. daily and five weeks ago stopped altogether since when she has had mepacrine 100 mg. daily for two weeks, then 100 mg. twice a week. She has remained very well—she says that she feels better than when on ACTH—and there has been no rise of temperature or other ill-effect. The B.S.R. is now 30 mm./hour (Westergren). The skin appears normal. The ECG has become normal. She has been discharged from hospital and is up and about.

12.9.52.—She is now back at work. No treatment has been given for the past six weeks.

Two Cases of Angioma Serpiginosum.—L. A. M. B. Musso, M.R.C.P. (for G. B. Dowling, M.D., F.R.C.P.).

This condition was originally described by Hutchinson (1889–90) under the title of "A Peculiar Form of Serpiginous and Infective Nævoid Disease", and given its present name by Crocker in 1893.

Case I.—S. G., female, aged 13 years.

The red spots, first noticed at the age of 6 years on the middle of the inner side of the left thigh, increased in number until about twelve months ago and not since. On the right thigh similar spots noticed two years ago. They are symptomless, and unaffected by the weather. The patient is unable to state the mode of spread of the lesions, and none seems to have disappeared.

On examination.—An area approximately 12·5 cm. × 11·5 cm., on the middle of the left thigh on the anterior and antero-medial aspects, consisting of purplish red, pin-point size, flat angiomatous lesions which are either discrete, or in groups of irregular shape, or have some tendency to be arranged in linear, or arc-like fashion. They are not emptied by pressure, and there is no associated erythema (*see* Fig. 1).

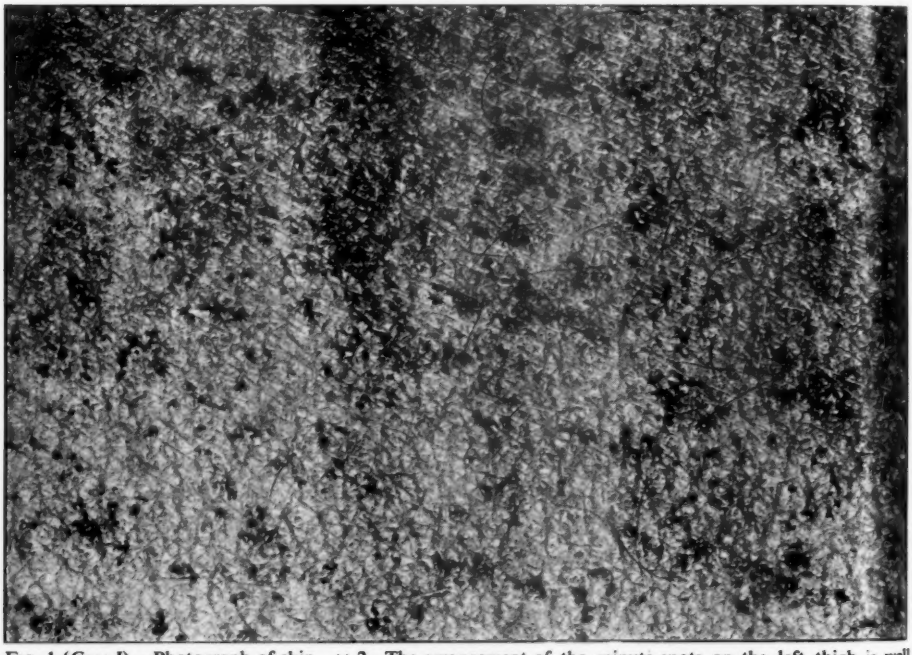

Fig. 1 (*Case I*).—Photograph of skin. × 2. The arrangement of the minute spots on the left thigh is well shown, viz. discrete, irregularly shaped groups, or with some tendency to arc-like formation.

A very small area on the front and upper aspects of the right thigh, consisting of a few discrete, and one group of the same angiomatous lesions is present. The skin concerned shows no other abnormalities, and no other vascular nævi were found on examination of the rest of the skin.

Case II.—I. B., female, aged 11 years.

First noticed red spots at the age of 5 on the back of the right leg, then at the age of 9 on the back of the right thigh, those on the right buttock being noticed at St. John's Hospital in June 1951. The spots are still spreading on the right thigh and right buttock. No symptoms but the spots are more prominent in winter. The mode of spread of the spots is unknown, and it is considered that none has disappeared.

On examination.—Over the right tendo achillis, and on the back of the right calf in an area 20 cm. × 5 cm. approximately, there is a partly reticulate network of red, pin-point size, flat angiomatous lesions with surrounding erythema. On the centre of the back of the right thigh, there is an area of 12·5 cm. × 12·5 cm. approximately, with a few outlying, discrete smaller lesions on the lower inner aspect, of mauve coloured, flat pin-point angiomatous spots, mostly discrete, though

some are in groups and one small ring is visible. On the right buttock there is an area of angiomatous lesions, similar to though generally smaller than on the right thigh, and without ring formation.

The spots do not disappear completely on pressure from any area, except on right calf.

Except for a livedo racemosa on the lower extremities, which is worse in winter, the skin concerned shows no further abnormalities, and no other vascular nævi were found on examination.

Comment.—These two cases are similar, though of different degree, and the following extracts will show that they fit in with the second and fourth cases described by Hutchinson, for only one or two rings were present to each patient:

Essentially in Hutchinson's first case (1889–90), a very slightly marked port-wine stain was observed at the back of the arm soon after the infant's birth. For some years it scarcely spread at all, and then began slowly to advance somewhat peculiarly, appearing as if little satellite spots had been produced which had spread into circles, and, by gradually advancing by infective edges, had coalesced, producing the irregular pattern which is here displayed. These conditions are no ordinary part of nævoid disease. They were extremely superficial, and it was even difficult to be sure whether or not they left any state of scar behind them. He had, however, no doubt that such was their tendency, and that in some places a slightly-marked, superficial scar could be demonstrated. The enlarged capillaries could be partially emptied by pressure, but not wholly, and in many places little tufts were distended with deep purple venous blood, which could be pressed out.

In the second case described by Hutchinson (1890–91*a*) in a patient of Dr. Allan Jamieson of Edinburgh, the arrangement of the lesions is in the form of minute puncta, some set closely together so as to form groups, others isolated, some arranged in lines. The individual puncta range in size from the diameter of a small pin, to points scarcely recognizable unless with the aid of a lens; the larger are a dark, the smaller a clear red. In the spaces between the grouped puncta, the skin is stained a faint pink. In one situation the puncta are clear and sharp, and have no intermediate staining.

In Hutchinson's fourth case (1891–92), a patient of Mr. Warren Tay, minute dots of deep red, or almost purplish tint, of variable size and very small indeed were closely placed, but, for the most part, discontinuous with each other, and not arranged in rings, or in any other definite kind of grouping. There was no evidence of any retrogressive changes, and not the slightest trace of scar could be detected. In a recent patch the dots were not so closely placed.

Hutchinson stated that a feature of difference in the fourth case from other cases of this malady was the slight tendency to form rings or crescents, which was marked particularly in Dr. Lassar's case cited by Hutchinson (1890–91*b*) and his own first case.

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—— (1890–91*a*) *Arch. Surg., Lond.*, **2**, 71.
—— (1890–91*b*) *Arch. Surg., Lond.*, **2**, 111.
—— (1891–92) *Arch. Surg., Lond.*, **3**, 166.

The President: Recently, some of us have seen in Germany a patient diagnosed as purpura annularis telangiectodes but without scarring, therefore not a typical example of Majocci's disease. It was, however, a typical example of the annular or serpiginous form of Hutchinson's disease.

Dr. J. E. M. Wigley: I do not recall having seen the condition in such young patients and at such an early stage before. One sees this condition usually in older patients when pigmentation has formed and the picture is much more confused.

? Reticulocytosis: Case for diagnosis.—A. D. PORTER, M.D.

G. H. F., aged 49. Married. No children. Previous occupation, soldier (served in India, Egypt and Turkey).

Complained of "Lumps in skin and difficulty in seeing".

Past history.—Jaundice 1930. Malaria, heat exhaustion, dysentery (? type), diphtheria, shingles, double inguinal hernia.

Family history.—All healthy apparently.

History of present attack.—First noticed painful lumps on soles of feet when serving in the Army in 1945. Fresh nodules soon began to appear elsewhere, especially on the face, neck and shoulders, and have persisted ever since. Although some nodules have disappeared and others become smaller, the condition has steadily progressed during the last few years. Pressure on the eyeballs has required surgical intervention on several occasions. Between two and three years ago "spots" appeared on the stomach.

On examination.—A well-developed man whose face is deformed by subcutaneous swellings, some of which press upon the eyeballs and have reduced the palpebral fissures to narrow slits. On palpation the swellings are felt to be firm, well-defined nodules lying within the subcutaneous tissue and attached to the skin. They vary in size from a few millimetres to several centimetres in diameter. The nodules are only very slightly tender and can be moved about freely on deeper structures, with the exception of certain nodules which appear to be attached to the upper ends of the tibiæ and may be of a different nature. In the umbilical and sacral regions are numerous discrete, firm, elongated papules, purplish-red in colour and between 1–10 mm. in length. The skin covering the nodules is normal in appearance. On the palate, near the uvula, there are a few deep-red infiltrated lesions. Apart from the condition described, no abnormalities were found except some pyorrhœa.

Investigations.—Blood count: W.B.C. 11,900. Neutros. 57%, lymphos. 31%, monos. 6%, eosinos. 6%. W.R. and Kahn reactions negative.

Skiagrams: Bones (skull, pelvis, knees and chest) normal; lungs normal. Serum cholesterol normal (167 mg./100 ml.).

Ophthalmic surgeon's report (Moorfields Hospital).—Vision = $\frac{4}{60}$ with restricted fields. Eyes are structurally normal, discs not pale. Difficult to explain the apparent visual defect.

Biopsy report (Dr. H. Haber).—There is a lobulated tumour replacing the fat tissue to a large extent. The stroma of the tumour is fibrotic and the tumour itself consists of a syncytium of reticulum cells of purple or pale colour. The cytoplasm is abundant showing granular to foamy appearance. The nucleus is round or oval and vesicular. There are also many bi- and multi-nucleated giant cells demonstrable. Some cells contain up to seven nuclei, all situated in the centre of the cytoplasm as in Dorothy Reed cells. There is also a marked admixture of inflammatory cells consisting of eosinophils, plasma cells, polymorphs, round cells and mast cells demonstrable. One or two mitotic figures could also be demonstrated.

Discussion.—The many hard, well-defined subcutaneous nodules which are yet attached to the skin make this case unusual. The feel of the nodules suggests that they might be formed largely of fibrous tissue, and this impression is confirmed by microscopic examination which shows them to consist largely of fibrous tissue and reticulo-endothelial cells. Many of the latter are "foamy" and some contain lipoid material. A few multi-nucleated giant cells are present and a mixed cellular infiltrate.

These appearances made three independent histologists diagnose xantho-fibromatosis. While this is perhaps an accurate histological description, it does not conform to the nature of the case clinically, which is certainly not that of any ordinary form of xanthomatosis.

The normal serum cholesterol and the lesions on the palate make one think of the eosinophilic xanthomatous granuloma of Tannhauser but the entire absence of xanthomatous lesions in the skin and other characteristic sites and the small amount of lipoid in the foam cells make such a diagnosis improbable. Other conditions giving a rather similar histological appearance, such as histiocytoma and tendon sheath tumour, can be excluded clinically, and there is nothing to suggest that the lipoid-containing foam cells are merely a secondary phenomenon such as may occur in any tumour.

Dr. F. Ray Bettley: I have seen this patient several times elsewhere and I cannot suggest a diagnosis.

Dr. H. Haber: The striking feature of this case is that the changes take place in the subcutaneous tissue. Histologically the lesion lies within the subcutaneous area and consists of reticulum cells in different stages of maturity, with storage of fat. Giant cells of the Dorothy Reed type and all types of inflammatory cells could also be demonstrated. If one considers that the fat tissue takes its origin from the reticulo-endothelial system, one can assume that we deal in this case with an anaplastic tumour of the fat, and consider the case to be lipoblastoma. I have not seen a picture like this before.

Sclerosing Lipogranuloma.—C. D. CALNAN, M.B., and H. HABER, M.D. (for J. E. M. WIGLEY, F.R.C.P.).

S. D., female, aged 33.

History.—November 1940: She was admitted to West Middlesex Hospital observation ward and transferred to Springfield Hospital, Tooting, because of an acute schizophrenic episode associated with the puerperium. Apparently the present skin lesions developed after this time though it is difficult to be sure whether they appeared within a few weeks or months or several years later. The injections she received when in hospital were morphia and hyoscine in aqueous solution.

She says that she has sometimes applied oil for insect bites on the arms and legs.

All the present lesions seem to have arisen at much the same time and there has been no progression or new eruption since she was first seen three years ago.

There was no fever or malaise.

Examination.—Mental retardation is evident. On the extensor surfaces of the arms and forearms is a more or less symmetrical distribution of bluish indurated and lumpy lesions of the dermis. They

vary in size up to 5 cm. in diameter. Several of them are altered by biopsy scars. They are fairly well defined, and there are no nodules distributed along the lymphatics, nor enlarged lymph glands.

On the extensor aspect of the thighs, and slightly on the shins, are similar symmetrical lesions, but the majority of these show atrophy of the epidermis with a mottled yellow surface and fine vessels, simulating necrobiosis lipoidica or scleroderma. They do not extend on the buttocks or any part of the pelvic girdle area.

Investigations.—Plasma proteins: Total 6·2 grammes/100 ml. Albumin 3·1 grammes, globulin 2·8 grammes, fibrinogen 0·3 gramme.

Histology.—Left arm: The epidermis shows slightly thickened stratum corneum of a basket-weave type. The stratum granulosum consists of one layer. The stratum spinulosum is slightly acanthotic and the papillary body is well developed. The collagen shows distinct thickening and homogeneization of its bundles, but appears in some places normal. The striking feature of the case is the presence of numerous cysts of different sizes giving the section a "Swiss cheese" appearance. The cysts show the following characteristics: Some appear to be round holes surrounded by collagen, some appear to be lined, endothelial-like, by a single layer of flat cells. Some of the lining cells show distinct vacuolation, or foamy appearance. Deeper towards the subcutis there are many large cysts surrounded by concentric rings of homogenized acellular collagen. The arrangement of the collagen is that of onion-skin shape. There is also a granulation tissue, chiefly arranged round blood vessels and sweat ducts demonstrable. It consists of loose and dense foci, of lymphocytes, large vacuolated histiocytes and a few mononuclear and multinuclear giant cells, with a foamy and vacuolated protoplasma. There are also numerous little vacuoles interspersed with the granuloma tissue somehow resembling the structure of leproma leprosy. In addition to this, numerous plasma cells are demonstrable, and they show different stages of degeneration leading to the formation of Russell bodies.

Left thigh: This section shows a similar appearance but for patchy extreme atrophy of the epidermis leading almost to erosion of the surface of the corium. Within the corium the large onion-skin shaped fibrotic rings round the cysts are missing. The granulation tissue is somewhat more developed. There are a few giant cells exhibiting typical asteroid bodies.

Comments.—It is impossible to obtain precise and consistent history from this patient because of her mental retardation. This has also been a major obstacle to the more thorough elucidation of her disease.

Although I have used the term lipogranuloma, I believe that my patient's condition should be separated from that of Dr. Anning's case shown here in November 1951, and which was similar to the group described by Smetana and Bernhard (1950). All of those, except one, involved the genitalia and pelvic region. I have seen 2 cases similar to mine in Leeds under the care of Dr. J. T. Ingram and Dr. A. J. E. Barlow. Others have been presented as scleroderma or paraffinoma. Much of this subject has been discussed in a recent monograph by Blanc of Geneva (1951), who has called them Liposcléroses Nodulaires Dysproteiniques since he regards the serum protein changes of primary importance.

The fat involved in the lesion in this case is abnormal in that it does not stain with osmic acid, and there is increased lipase activity over the area of the granuloma. There is no evidence of spontaneous resolution.

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The following cases were also shown:

Urticaria Pigmentosa.—Dr. W. J. O'DONOVAN.

(1) **Erosive Gingivitis—Lichen Planus of Mouth and Vulval Skin.** (2) **Morphœa-like Epithelioma.** (3) **Ichthyosiform Hyperkeratosis with Malignant Glands.**—Dr. L. FORMAN.

Norwegian (Crusted) Scabies.—Dr. D. S. WILKINSON.

(1) **Striate Lichen Planus.** (2) **Lichen Striatus.**—Dr. HAROLD WILSON.

(1) **Cutaneous Eruption in a Patient with Filariasis Loa-loa.** (2) **Case for Diagnosis.**—Dr. J. S. PEGUM.

Pityriasis Rubra Pilaris.—Dr. P. J. FEENY.

Primary Tuberculous Complex.—Dr. BRIAN RUSSELL.

Leucodermia and Psoriasis.—Dr. S. GOLD.

(These cases may be published later in the *British Journal of Dermatology*.)

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Section of Surgery

President—DAVID H. PATEY, M.S., F.R.C.S.

[*March* 5, 1952]

Patent Ductus Arteriosus

By DENIS BROWNE, F.R.C.S.

OPERATIONS for the removal of structures which should have atrophied before birth in the strange processes of the formation of the human body are naturally among the most satisfactory in surgery. At the price of an operation and a scar such abnormalities as the sac of an inguinal hernia, a dermoid cyst, or a branchial fistula can be obliterated, to leave the body as it should have formed originally. Among such operations perhaps the best of all is that for ligature of a persistent ductus arteriosus, as before this was practised the sufferer had only too likely a prospect of a life of invalidism and an early death.

To gain the full benefit of operation it must obviously be performed early, so that during as much as possible of the growing period the body may have the benefit of a normal blood flow, and in addition the almost inevitable later infection may be avoided. The technical difficulties caused by the smallness of the patient are more than counterbalanced by the ease of dissecting out the ductus in tissues that have the mobility of extreme youth and have never been inflamed.

The series described in this paper consisted of 80 cases, some 15 of which were operated upon by Mr. David Waterston, and the rest by myself. Their ages ran from 15 months to 14 years, 4 of them being under 2 years of age: operation upon the very young cases was advised because of signs of cardiac embarrassment. There were no deaths, and all the cases except one derived the hoped-for benefit. In this unsatisfactory case a murmur persisted which is believed to be due to some congenital anomaly apart from the persistent ductus. In one of the early cases, in which the approach was made through an anterior incision, the operation was abandoned because of the difficulties caused by a very large thymus. The ductus was later ligatured without difficulty through the axillary approach, to be described.

Recanalization has not so far occurred in any case. The time of operation has run consistently at just under an hour.

The main point of technical interest is the approach used, through the axilla. I originally tried this because I was worried over the disfigurement caused to patients by the usual anterior or posterior incisions; the former especially ruining a most important area for the girls who form the majority of the cases. To my surprise and satisfaction I found that the access gained in this way was better than that by either of the other routes. After all, if one were exposing the ductus through a chest wall from which muscles and scapula had been stripped, the obvious approach would be through the third interspace; and with the technique used this interspace is opened up throughout its entire length. Admittedly this axillary approach depends on the use of my pattern of retractor, which has certain original points about it. The first frame retractor I ever saw was Devine's model, but this did not seem to me to have exploited the possibilities of the principle. I think the reason for the slowness of both instrument makers and surgeons to appreciate the almost universal usefulness of such an instrument (it is the best I know for cleft palate and mastoid operations, as well as chest, neck and abdominal ones) is that the incision in the patient is an essential part of the mechanism, and in consequence the metal parts fall apart and look absurd on a shop counter.

Its action is, so to speak, to claw a way downwards through the successive anatomical layers encountered. It will be noted that four different planes have been successively picked up and are simultaneously retracted in the operation described; the skin and subcutaneous tissues, the muscles and the scapula, the ribs, and finally the lung itself. Any structure can be retracted in any desired direction, and by the use of the screw blades with any necessary amount of force and delicacy of adjustment. One of the most helpful features of this system is that one's assistant is thus freed for the really important work of assisting tricky manipulations in the depths of the wound, rather than being immobilized in a task much better fitted to a fixed mechanism.

TECHNIQUE OF OPERATION

(1) The incision runs down the posterior border of the axilla (Figs. 1–4).

(2) The borders of the latissimus dorsi and the pectoralis major are defined and retracted.

(3) The serratus magnus is divided with a diathermy needle in the line of the skin incision. This allows the main part of the muscle, complete with nerve supply, to be retracted outwards from the chest wall, carrying the scapula with it. The freedom of this movement is one of the surprises of the operation.

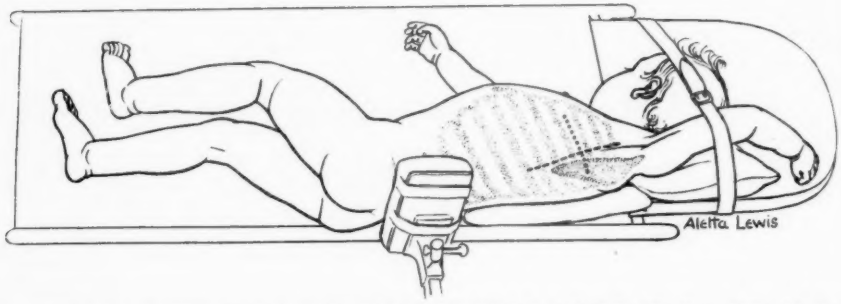

FIG. 1.—Position of child on operating table, which is tilted slightly to the left. The lines of the skin incision and that in the third intercostal space are shown. The intercostal incision is finally lengthened to close against the vertebral column.

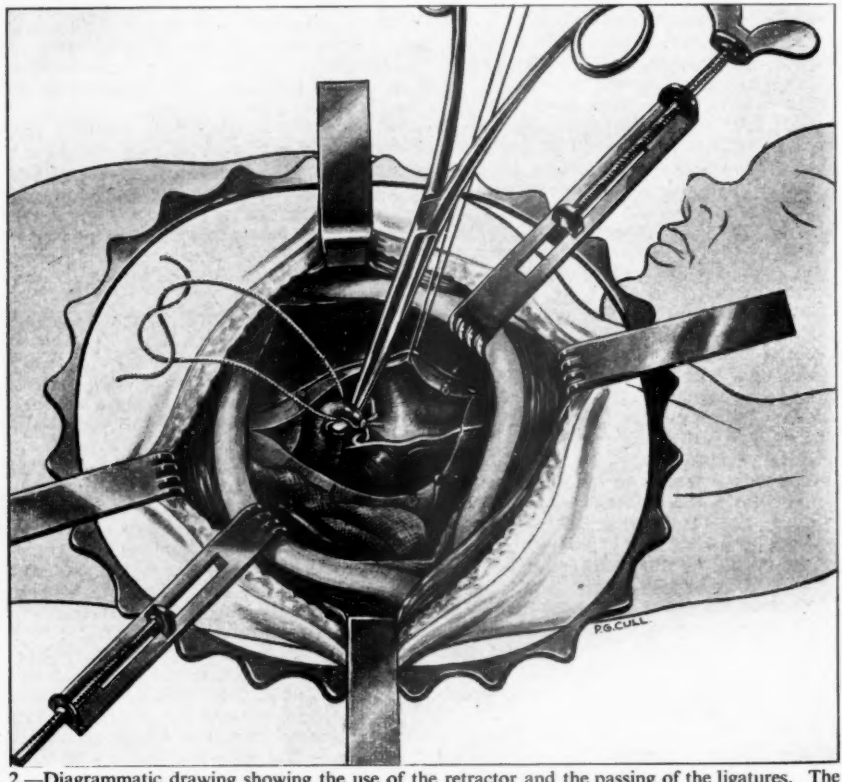

FIG. 2.—Diagrammatic drawing showing the use of the retractor and the passing of the ligatures. The ends of the "divulsors" are actually much finer than is shown.

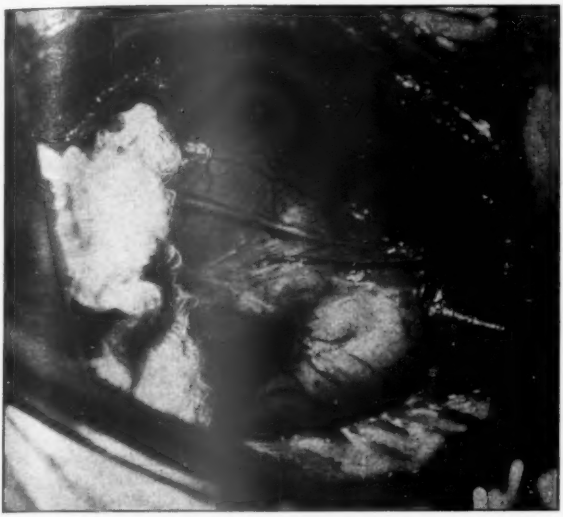

FIG. 3.—View of the mediastinum obtained by the approach described. In this operation an ordinary rib-spreader was used instead of the screw retractor blades shown in Fig. 2.

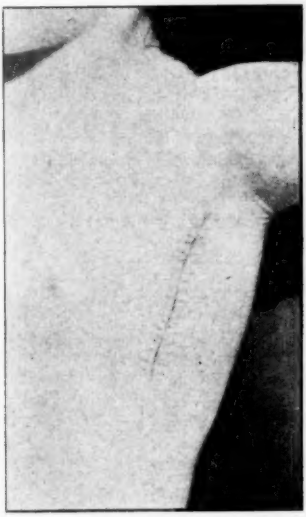

FIG. 4.—After removal of stitches, showing line of scar.

(4) The pectoral muscles are dissected free from the chest wall by the diathermy needle, until they can be retracted sufficiently to expose the cartilage of the third and fourth ribs. Care is taken to avoid the nerve supply.

(5) The exposed length of the intercostals of the third interspace is divided with the diathermy needle. The screw retractor is applied, and the lung collapsed with a gauze pack, held by a long flexible blade.

(6) The posterior part of the intercostals is then divided by the diathermy needle from the inside of the thoracic cavity, and the ribs retracted to the fullest extent possible. This interior division of the intercostals is an important part of the approach.

(7) The azygos vein is ligatured and the ductus dissected out by means of "divulsors". These are long forceps specially designed so that tissues can be split by thrusting in the points and then separating them. One pair has the ends bent at right angles, and the other at 45 degrees. With these it is possible to clear the back of the ductus rapidly and safely, and then to grasp and pull round the ligatures. They are held by the surgeon in the "ulnar position", not in the more ordinary "radial position" used for artery forceps, &c., in which the ends point away from the radial side of the forearm. The effort needed to acquire familiarity with this grip is well repaid by the unobstructed ease of working at depth which it gives. In most cases a thread passed through the upper edge of the incision in the pleura and tied on to the frame of the retractor so as to lift the phrenic nerve and its surrounding tissues forwards will add to the ease of access.

(8) Two lengths of thick plaited silk are passed round the ductus and tied with the greatest possible tightness. An important point is that no attempt is made to dissect the wall of the ductus clean of adventitious tissues, or of any extension of the pericardium which may overlie it. It is considered that once the recurrent laryngeal nerve is seen to be clear, the more tissue that is included the safer the necessary tight ligature becomes.

(9) A fine urethral catheter with several holes punched near the tip is put in along the posterior sulcus of the thoracic cavity, and the ribs brought together by three or four thick catgut sutures. These are inserted by a two-thirds circle needle with a blunt probe end, which avoids the risk of perforating an intercostal vessel.

(10) The divided serratus is carefully sutured. Probably the small part anterior to the line of division is rendered inert by the cutting of its nerve supply, but it is impossible to detect this clinically afterwards. The skin is closed by fine interrupted sutures.

(11) The catheter is connected up to a "double flask" suction apparatus of the kind described in "Neo-natal Intestinal Obstruction" (Browne, D., 1951, *Proc. R. Soc. Med.*, **44**, 623). This is an

insurance against accidents from leakage of either air or blood, and gives interesting information of the process of healing in the chest. Usually from 10 to 30 c.c. of blood-stained serum comes away in the first twelve hours, the flow rapidly ceasing thereafter. When it has ceased the catheter is removed, usually in twenty-four to thirty-six hours. Though many of the early cases were treated without this drainage it is considered that there are no objections to it, and certain advantages in its use. It is certainly both more effective and informative than the "water-seal" type of drainage of the chest, in which it is impossible to see the amount and rate of discharge, or indeed whether (as not infrequently happens) there is no suction acting on the pleural cavity at all. This type of suction on a cavity, which consists in using the universally available weight of the atmosphere as a pressure dressing, can be used in any operation in which a potential dead space is produced, and in our experience is a great help to rapid healing.

(A cinematograph film was shown to illustrate the operation.)

My thanks are due, first, to Dr. Bonham Carter, whose diagnosis of the presence of a persistent ductus was correct in every case. Secondly to the anæsthetists, particularly to Dr. David Aserman, to whose skill in keeping small patients under control with very small amounts of anæsthetic the remarkably good post-operative condition of the cases is due. I may say that he shares my own dislike and mistrust of muscle relaxants of the curare type in the young and never uses them on my cases. Finally there is the nursing staff, particularly Sister Crittall, to whose unremitting care the complete absence of post-operative complications has been largely due.

Mr. E. M. Nanson (Bristol) mentioned some ducts which he considered should be divided rather than tied. These were large atypical ducts associated with pulmonary hypertension. Also he thought that suction drainage should not necessarily be adopted. Indeed in many cases any drainage was unnecessary.

Mr. G. Qvist (London) asked if any winged scapulæ developed as a result of Mr. Denis Browne's operation.

In reply **Mr. Denis Browne** said that suction drainage provided the equivalent of a pressure dressing. The amount of fluid coming out appeared to justify suction.

None of his patients had developed winged scapula.

Portal Venography

By Alan H. Hunt, M.Ch.

It is not possible to complete the investigation of a case of portal hypertension until the abdomen has been opened. Then it is necessary to examine the liver, the spleen and its attachments, the nature and extent of the collateral anastomotic channels, and to estimate the portal venous pressure. In doing this it is usually possible to determine the site of the obstruction. Venography, however, is essential to show the extent of the obstruction; the state of the portal venous tree (Fig. 1); where the main veins are situated; what sort of varicose transformation has occurred if the obstruction is extra-hepatic; whether or not portal thrombosis is present in addition to cirrhosis; and where the bulk of the portal blood is flowing. It is also of value in testing a previously constructed portal-systemic anastomosis and may also provide evidence for or against the effectiveness of other operative procedures such as gastro-œsophageal resection or gastric transection (Hunt, 1952).

Our knowledge of the underlying pathological processes is as yet by no means complete. Conclusions based on false premises are apt to be wrong. Often, therefore, more than one operation has to be done in an attempt to stop recurrent hæmorrhages or to alleviate ascites. Since we are not as yet by any means sure of our position, I think that venography should be done in almost every case, so that, if things go wrong, a record of the functional anatomy of the portal vein is made at each operation. In about 4 out of 5 cases, venography is not absolutely necessary, but in the fifth case it is essential. It is never possible to be certain that venography will not be of assistance.

It has been argued that the only way of being sure of the state of the portal or the splenic vein is by dissection. Ultimately this is true, but surgeons who are familiar with this type of surgery know how tedious, finicky and dangerous such dissections can be, especially when the normal anatomy is distorted. A venogram not only demonstrates what the main portal venous channels are like, but shows where they are and how they are functioning. Indeed, sometimes venography is required to demonstrate whether there is a reasonable portal venous channel at all. I refer to those patients with extra-hepatic obstruction with cavernoma formation whose spleens have previously been removed.

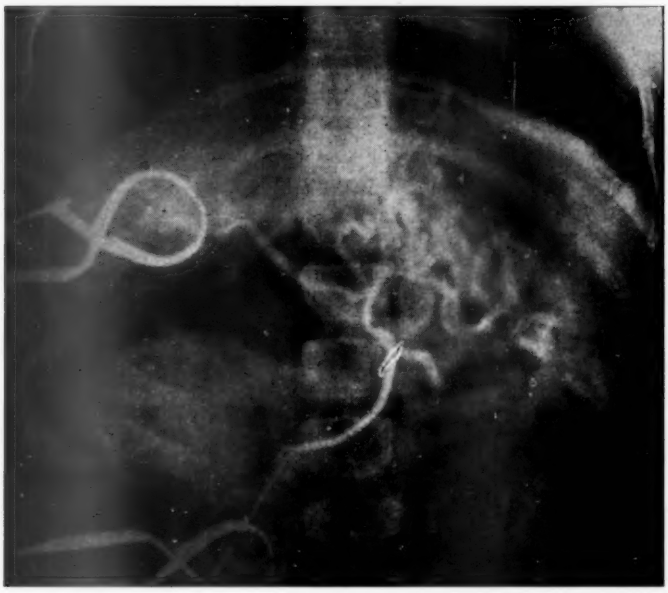

FIG. 1.—Venogram at operation. The portal vein is constricted but normally situated. Only a short segment of splenic vein remains patent.

It would be of great value if the venogram could be done pre-operatively. It is occasionally possible to demonstrate the portal vein during the course of aortography. I have no experience of this procedure, but Professor Alan Johnstone of Leeds has informed me that he has tried it in several cases with clinical evidence of portal hypertension and in none was he able to get any idea of the point of portal obstruction.

The simplest and quickest method at operation is to select a suitable vein after taking portal pressures, and inject as rapidly as possible 30 c.c. of 70% diodone. A 50 c.c. syringe should be used, and the needle should be as large as can conveniently and safely be inserted into the vein. The exposure should be made at the end of the injection. The whole process takes no more than two or three minutes. The film should be in a cassette tunnel under the patient and placed to cover the area from the level of the nipples to that of the umbilicus. The exposure should be determined by a trial X-ray taken before operation. For children the quantity injected should be reduced in proportion to their size. No ill-effects have been observed. (Diodone dries out quickly, so the syringe should not be filled until everything is ready for the injection.)

The method is not original or new. It has been advocated by Blakemore and Lord (1945), Learmonth (1947), Auvert (1951), and by Santy and Marion (1951), who reproduce some excellent pictures obtained by their method of injecting the dye into a branch of the splenic vein after ligating the splenic artery.

I am grateful to the staff of the Diagnostic X-ray Department at St. Bartholomew's Hospital for their co-operation.

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The Investigation of Peripheral Vascular Disorders

By PETER MARTIN, M.Ch.

THE objects of investigations into the peripheral vascular tree are to obtain an estimate of the degree of arterial insufficiency, if any, to estimate which case will be benefited by any particular form of treatment, and to assess improvement following treatment. There is little to be learned from most tests, unless the circulation in a limb is at its maximum, for in a cool room with a limb at rest, the measured flow differs little from the flow in a severely ischæmic limb. It is only when the circulation through the tissues to be tested is at its maximum that defects will be seen. It is therefore necessary to achieve the maximum flow, and this is simple where muscle flow is being tested and is achieved by a standard exercise while the circulation of a limb is occluded when, after release of the tourniquet, a maximal flow is obtained. In the skin and subcutaneous tissues functional sympathetic release can be simply but incompletely achieved by reflex heating, but probably complete release, simulating that achieved by sympathectomy, can only be obtained by peripheral nerve block as by anæsthetic block of the ulnar or posterior tibial nerves. Other methods such as spinal or general anæsthetic, Priscol and paravertebral sympathetic block are less useful as a routine owing to associated alteration in blood pressure or the comparative difficulty of the technique. The methods we have used extensively are: (1) Skin temperature tests. (2) Plethysmography. (3) Oscillometry. (4) Circulation time by injection of fluorescein. (5) Arteriography.

Skin temperature tests are useful and easy, provided their limitations and errors are appreciated. Prolonged body heating, even up to sixty or ninety minutes, may not result in full vasodilatation if the room temperature is low, and may give rise to a false assessment. Fig. 1 shows the skin temperature of the same limb in a room temperature of 17° C. and a room temperature of 23° C. Secondly a high toe temperature can be reached in a leg which is obviously nearly gangrenous, and thirdly, distal temperatures may not begin to fall until the circulation is quite deficient.

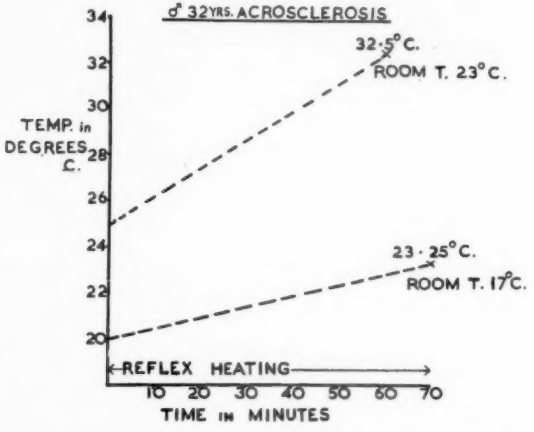

FIG. 1.—The results obtained from reflex heating depend to a large extent on the room temperature.

Plethysmography, using the technique described by Barcroft, can be applied to the calf or forearm when flow in muscle is measured, or to the foot or hand when flow in skin or subcutaneous tissues is being considered. The results in skin follow generally the skin temperature tests, but much more accurately, and a quantitative blood flow in c.c. per 100 c.c. tissue per minute is obtained. In muscle after release of the tourniquet there is a rapid and remarkable rise, and the return to normal flow is equally rapid, but in a limb the site of arterial disease, the rise is slower and less marked, and the return to normal is considerably delayed, and quite small deficiencies are readily detected (Figs. 2A and 2B). The drawbacks to the method are the difficult apparatus necessary, and the time taken over each test.

Dr. Denis Melrose has thought out and built for us an electronic method of recording oscillations, and we have applied this to the study of digital oscillations. Fig. 3 shows the effect of temperature on the terminal phalanx of an elderly gentleman of 81 years, and the nature of the pulse wave gives considerable information as to the state of the arteries shown by the dicrotic notch (Fig. 4). It must,

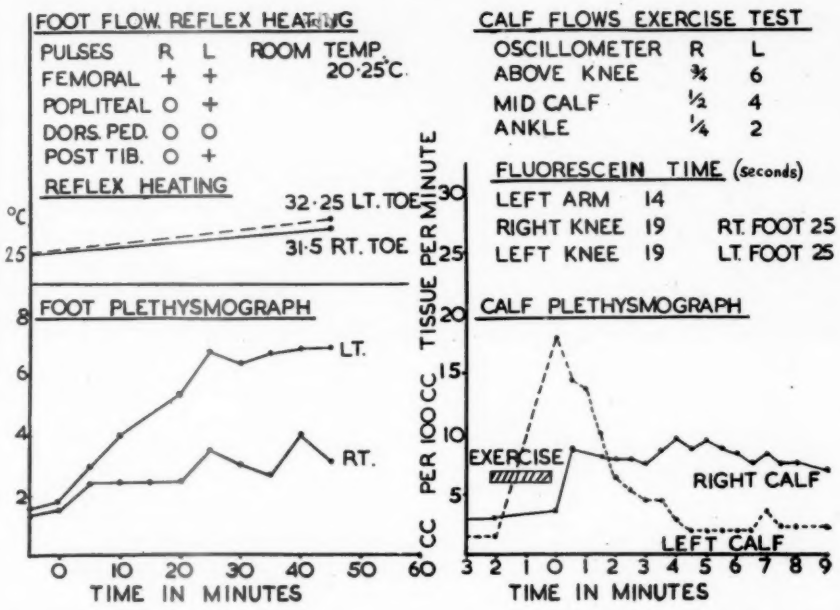

FIG. 2A.—The calf plethysmograph shows diminished and delayed increase in flow in the right calf following exercise with a marked delay in return to normal. Compare this with Fig. 2B which shows a sharp rise and sharp fall in a normal circulation.

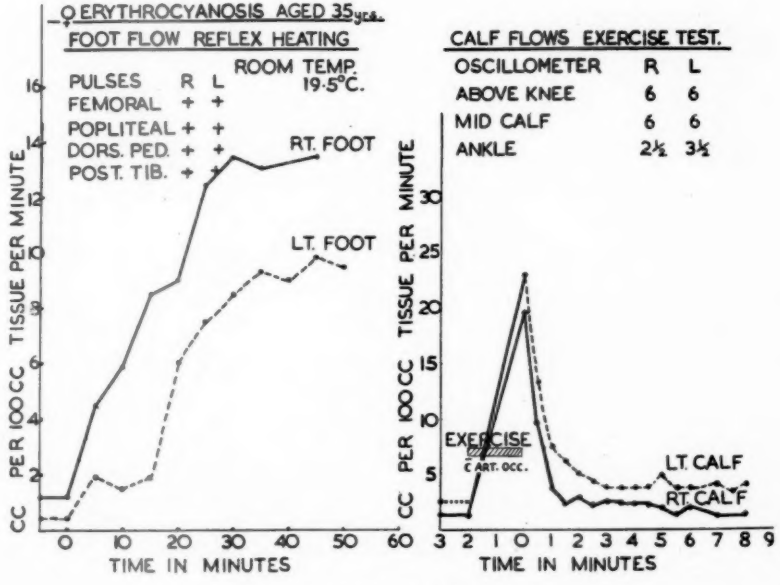

FIG. 2B.—Normal calf flow following exercise.

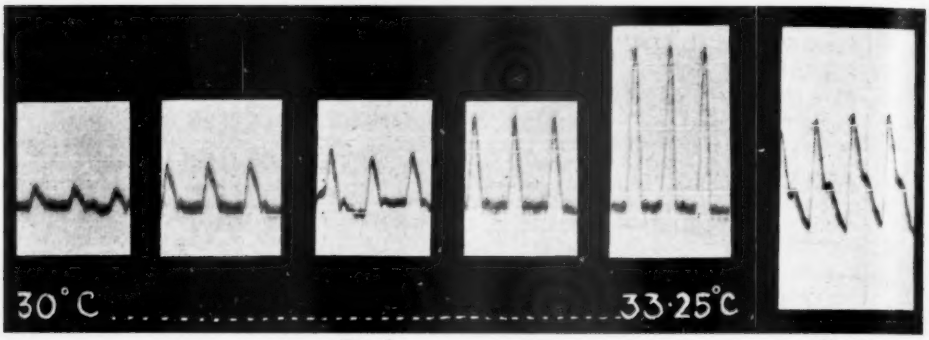

FIG. 3. FIG. 4.

FIG. 3.—Oscillometric recordings from the distal phalanx of a male aged 81.

FIG. 4.—Oscillometric record from the distal phalanx of a healthy female of 19. There is a marked dicrotic notch.

FIG. 5.—The angle of the slope through the pulse waves indicates the flow of blood through the phalanx.

FIG. 6.—Arteriogram of an arteriosclerotic lower limb.

FIG. 5.

FIG. 6.

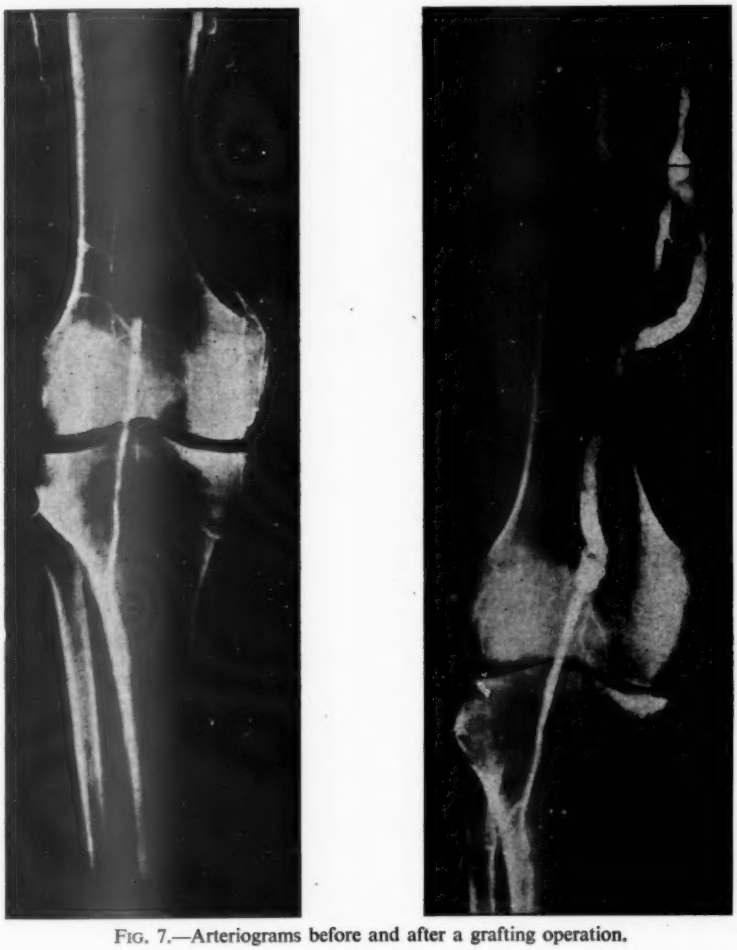

FIG. 7.—Arteriograms before and after a grafting operation.

of course, be appreciated that the absence of oscillations does not mean absence of blood flow, as an obstruction in a major vessel in the more proximal part of a limb may cause diminution or disappearance of oscillations, where the collaterals provide a perfectly adequate flow distally. Also swelling of a limb from lymphœdema or other cause will mask oscillations. In these cases Dr. Melrose has produced an attachment to the apparatus which will give a quantitative flow in a distal phalanx of the hand or foot (Fig. 5).

Circulation time.—The fluorescein method has given considerable help, but it is not as sensitive as plethysmography and its value has not yet been fully assessed. Its value is on a par with skin temperature tests.

Arteriography.—Great value is placed on an arteriogram of the whole limb (Fig. 6); a visualized segment of the arterial tree is of less value. Pyelosil 50% is injected into the femoral or brachial arteries percutaneously under pentothal anæsthesia, and a radiological technique perfected by Dr. R. E. Steiner is used. From the arteriogram is judged the general state of the vessel, the site of major blocks, and these are very often multiple, the adequacy of the collaterals, and the filling or otherwise of more distal vessels. We have believed for some time that any real advance in the treatment of peripheral arterial disease will require local surgical attack on obstructed vessels, and in such cases careful evaluation of the whole arterial tree of a limb by radiography is essential. For example, a blocked segment in a major limb vessel may be by-passed by a graft of autogenous vein (Figs. 7 and 8).

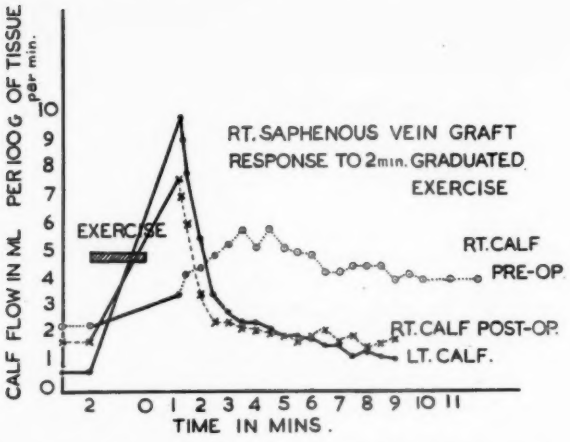

FIG. 8.—Note the right calf flow following a grafting operation has returned to its normal pattern. This patient's claudication was cured.

Finally a history of the case, together with a careful clinical examination taken in conjunction with the results of various laboratory tests, will give a picture of the circulation as a whole, an indication of the treatment which is proper, an estimate of what can be achieved and a prognosis of value.

Professor J. H. Dible described with photographs of injection specimens the results of progressive ischæmia leading to gangrene. The variations in the vascular pattern were enormous.

Mr. H. J. McCurrich described a method of taking skin temperatures seriatim with ten electrodes attached to each limb and a series of switches so that the skin of the limb did not have to be handled nor the electrodes reapplied during the investigation. By eliminating variable factors due to handling the skin or varying pressure due to changing and holding electrodes against the skin considerable improvement in accuracy and constancy was obtained in plotting the effects of spinal anæsthesia, ganglion anæsthesia, and intravenous Priscol.

Mr. Frank Forty asked how accurate information about muscle blood supply might be obtained.

Dr. J. F. Goodwin said that there was little doubt that Priscol acted locally on the vessel wall, in addition to its other effects. Lynn (1950, *Lancet*, ii, 676) had shown that interarterial injection in a denervated limb resulted in an increase in blood flow. This action suggested a rational basis for the use of Priscol after sympathectomy.

Mr. Peter Martin in answer mentioned that Priscol is more effective after sympathectomy and that he considered that heating the patient was better as a method of obtaining peripheral vasodilatation than spinal anæsthetic or paravertebral block.

Professor Dible pointed out that the circulation through muscles is not organically obstructed in claudication, but that the symptoms are due to a general circulatory stagnation.

Section of Urology

President—ARTHUR JACOBS, F.R.F.P.S.

[*April* 24, 1952]

DISCUSSION ON UNILATERAL RENAL HYPERTENSION

Dr. J. H. Wright: The normal blood pressure of an adult at rest, comfortably warm and unperturbed, is in the region of 120 mm. mercury systolic and 80 mm. mercury diastolic. The ratio between systolic-diastolic and pulse pressures is normally 3 : 2 : 1.

A systolic pressure constantly above 150 mm. mercury is regarded as systolic hypertension, and a diastolic pressure of 95 mm. mercury, or over, as diastolic hypertension.

When we speak of hypertension, we usually mean diastolic hypertension. It is this type which is intimately associated with arteriosclerosis—an association as intimate as that of the hen and the egg, and as puzzling with regard to priority.

The ætiology of diastolic hypertension.—There are several possible factors in the production of hypertension: blood volume, blood viscosity, arteriolar contractility and arterial rigidity; but it is generally accepted that the only important factor is arteriolar contractility.

Contraction of the muscular medial coat of the arteriole may be influenced in several different ways.

Neurogenic.—Stimulation of the sympathetic nervous system leads to constriction of arterioles.

There is a depressor mechanism with afferent fibres in aorta and carotid arteries—distension of these vessels leading to reflex peripheral vasodilatation—the so-called aortic sinus mechanism.

Emotional upset does not cause a simple reflex stimulation of either the sympathetic pressor or the aortic sinus depressor mechanism. 5 patients, apparently under emotional stress, may show five different results: The first may show systolic hypertension; the second, both systolic and diastolic hypertension; the third, diastolic hypertension without systolic hypertension; the fourth may have no significant variation of either systolic or diastolic pressures; and the fifth may have a lowering of both systolic and diastolic pressures, usually accompanied by a slowing of heart rate.

Neurological control is complex and the response to emotional upset is not always predictable.

Endocrine.—Following the observations of Oliver and Sharpey-Schaefer, it was accepted that the secretion of the medullary part of the suprarenal (adrenaline) caused vasoconstriction indirectly by stimulation of the sympathetic mechanism and also by direct action on muscle, but recently it has been shown that the main action of adrenaline is on the heart, causing increased rate and increased force of contractions, and that its action on the peripheral vascular system is that of a vasodilator. The medullary part of the suprarenal contains varying amounts of noradrenaline, which has little action on the heart and which causes vasoconstriction.

Certain secretions of the cortical part of the suprarenal, especially desoxycorticosterone, are capable of producing vasoconstriction; this pressor action is, to some extent, dependent on the presence of adequate blood sodium and, as the kidney helps to control blood sodium level, it plays some part in the pressor action of the cortical part of the suprarenal.

The pituitary can also produce pressor actions—the anterior part probably does so indirectly by affecting the activities of the glands of internal secretion; the posterior part probably has a direct pressor action.

Renal.—Bright was well aware of the existence of some close relationship between chronic renal disease and cardiovascular degeneration.

The introduction of methods of recording blood pressure soon led to the recognition of an association between renal disease and hypertension.

Goldblatt and others have shown that renal ischæmia can cause hypertension and that in the early stages, at least, the hypertension is due to some substance in the damaged kidney which passes out into the general circulation via the renal vein.

There is still no general agreement as to what this substance is, or how it acts: It may be a pressor substance produced by the ischæmic kidney; it may be due to vasoconstrictor amines which accumulate because of the failure of the kidney to de-aminize them; it may be due to failure of the kidney to act on and neutralize a pressor substance already in the circulation.

We accept that disturbance of kidney function can lead to hypertension, but we do not know how it does so.

Clinical hypertension cannot be pigeon-holed in the same way as experimental hypertension.

Most sufferers from hypertension are said to have something called "essential" hypertension—I have never understood why disease or degeneration should be complacently accepted as "essential", and I prefer the term idiopathic.

Renal dysfunction, and particularly the dysfunction secondary to ischæmia, can lead to hypertension, but we still do not know how or why. The removal of a diseased kidney, as treatment for hypertension, is, to some extent, an empirical measure.

Let us now pass from the realms of theory to the practical problems of unilateral renal disease and hypertension as they confront the physician.

There are two main problems:

(1) When should the physician seek the help of the urological surgeon in the investigation of a patient with hypertension?

(2) If urological investigations reveal the presence of a unilateral renal lesion in a patient with hypertension, what are the indications for nephrectomy?

It is important to keep in mind that unilateral renal disease is a rare cause of hypertension (*see* Tables I, II and III).

Patients with hypertension might be considered to fall into 4 groups (I shall exclude coarctation and phæochromocytoma from the discussion):

(1) Those with symptoms and signs suggestive or indicative of a surgical lesion of kidney—hypertension being an incidental finding.

(2) Those who seek advice because of hypertension, and in whom general examination reveals evidence indicative or suggestive of a surgical renal lesion.

(3) Those who seek advice because of hypertension and in whom general examination reveals evidence suggestive of chronic nephritis.

(4) Those who seek advice because of hypertension, and in whom general examination gives no indication of renal involvement.

The physician has no difficulty in dealing with patients in the *first* group. They are sent to the urological surgeon for investigation and, if a surgical lesion is found, the decision for or against operation will depend on the type of lesion—the presence of hypertension will play little or no part in affecting the decision.

Those in the *second* group should also have the benefit of full urological investigation, provided there is no azotæmic kidney failure, or cardiac or cerebral complication of sufficient severity to render investigation undesirable or dangerous.

As in group (1) the decision for or against operative treatment would depend on the type of lesion found. The presence of hypertension would affect this decision only because of increasing the hazard of operation.

Patients in the *third* group should have full urological investigation if they are under 40 years of age, and have no signs of severe azotæmic renal failure. Investigation is especially indicated in those whose history and signs raise the possibility of pyelonephritis.

In the *fourth* group, those under 40 years should have full urological investigation.

It is most unlikely that one will meet with unilateral renal disease as a cause of uncomplicated hypertension in patients over 40 years of age and especially in those with a strong family history of hypertension.

If unilateral renal disease is discovered in a patient in groups (3) or (4), there are some generally accepted arguments for or against nephrectomy. There should be evidence of considerable disturbance of the affected kidney's function—slight pyelonephritis or slight hydronephrosis are considered to be unlikely causes of hypertension. There should be no evidence of any considerable disturbance of function of the other kidney.

Severe azotæmia is a contra-indication to nephrectomy.

Patients over 50 years of age are unlikely to have their hypertension improved by nephrectomy.

Severe vascular complications, especially cardiac or cerebral, usually render nephrectomy undesirable; vascular retinal changes, even of some standing, are no contra-indication to operation.

The ideal case is the young patient with unilateral chronic pyelonephritis, the other kidney being unaffected.

TABLE I.—UNILATERAL RENAL ATROPHY OR HYPOPLASIA

Glasgow Royal Infirmary Pathology Department.
January 1942–March 1952 (Prof. Geo. Montgomery)

(1) *Found at Post-mortem Examination* (3,589 *Autopsies*)

Cause of atrophy	No. of cases	Pathological evidence of hypertension	Clinical Hypertension + ve	− ve	Not noted
Chronic pyelonephritis	28	19	14	6	8
Renal tuberculosis	2	1	1	1	—
Renal actinomycosis	1	1	1	—	—
Pyelonephritis + ureteric obstruction ..	10	5	2	1	7
Ureteral obstruction alone	3	1	1	—	2
Vascular disease alone	18	14	8	—	10
Congenital hypoplasia	3	1	1	2	—
	65	42	28	10	27

(2) *Found at Routine Biopsy Examination* (28,933 *Biopsies*)

31 unilateral small kidneys examined—all pyelonephritic.
Clinical hypertension noted in 7. Renal arteriosclerosis noted in 17.
Blood pressure normal in 1. Absence of renal arteriolosclerosis noted in 1.

TABLE II.—OUT-PATIENTS: JANUARY 1946–JANUARY 1948
(Prepared by Drs. E. A. Marshall and R. Fife)

Total Number of Patients	2,645		
Normal blood pressure	1,521	Male	857
		Female	664
Raised diastolic pressure	1,124	Male	577
		Female	547
16 had signs of renal disease:			
Nephritis (chronic)		Male	5
		Female	4
Pyelitis		Male	1
		Female	3
Hydronephrosis		Male	1
		Female	1
Stag horn calculus		Female	1

TABLE III.—IN-PATIENTS (GLASGOW ROYAL INFIRMARY)

Age groups	Total M+F	Male Total	Male Idiopathic Fixed	Male Idiopathic Labile	Male Renal Fixed	Male Renal Labile	Female Total	Female Idiopathic Fixed	Female Idiopathic Labile	Female Renal Fixed	Female Renal Labile
0–30	12	5	0	1	2	2	7	0	2	3	2
31–40	52	22	3	13	4	2	30	11	18	1	0
41–50	119	47	21	19	3	4	72	22	35	8	7
51–60	143	56	17	32	3	4	87	29	46	8	4
61–70	93	27	9	14	2	2	66	19	41	3	3
71+	38	26	14	9	1	2	12	1	11	0	0
Total	457	183	64	88	15	16	274	82	153	23	16

Mr. A. I. L. Maitland: Ten years ago when Heritage (1942) opened the previous discussion on this subject experience in this country was confined to a few cases. Through the co-operation of members of the Section 146 cases of unilateral renal hypertension whose treatment has passed a year have been collected for this discussion.

The standard which has been adopted for assessing the results is a high one. A result has been classed as good only if the diastolic pressure has remained at, or under, 100 mm.Hg for over a year. Exceptions

have been made in one or two cases where the elevation above this figure has been small and the period of observation prolonged. All other results have been classed as bad. This arbitrary standard has been adopted for two reasons. It simplifies tabulation and is also defensible on clinical grounds. Continuing diastolic hypertension indicates that the suspect kidney has not been the sole cause of the hypertension and that the opposite kidney has been affected, either by the hypertension or by disease, or the hypertension has had its primary cause outwith the renal tract. Such continuance exposes the patient to cerebrovascular or cardiovascular crises and the loss of a kidney increases twofold the danger of death by renal failure. Continuing hypertension without symptoms occurred in 19 cases and, for the reasons given, most of them have been added to the bad results.

Hypertension is a common condition but that due to unilateral renal disease is relatively rare. In two large American series only 5·5% (Ratliff *et al.*, 1947) and 4% (Braasch, 1942) respectively showed unilateral renal lesions, and of these fractions less than half in the former and less than one-fifth in the latter had a kidney removed.

Unilateral renal hypertension is more common in females than in males and in the latter appears to have a slightly better prognosis.

The condition is found in all age groups. Below the age of 30 years more good results than bad may be expected; in older age groups the proportion is reversed but remains much the same in the later decades, and even the elderly patients offer a chance of successful treatment if the cases for operation are chosen with care.

The condition is associated with symptoms referable to the renal tract in rather less than half the cases, the discovery of hypertension initiating an investigation of the renal tract in the remainder. Cases collected from the literature (69) show a higher number of good results in those presenting as hypertension primarily and without renal symptoms. In the present survey this has not been so and it is felt that this difference may be related partly to the large number of cases of hydronephrosis which it contains and partly to a difference in the methods of examining renal function.

The length of the history does not appear to be significant in relation to the result obtained. In 51 cases previous renal disease or complications of pregnancy occurred and the greatest care is required to prove in such cases that the disease is unilateral before a choice of treatment is made. This applies particularly when the hypertension is unaccompanied by renal symptoms.

In 56 cases some abnormality of the optic fundi was discernible on retinoscopy. This group of cases reveals that papilloedema, in the absence of exudates, offers a better prognosis than those cases in which exudates are present, and, rather more surprising, it reveals that the prognosis is also better than in those cases in whom retinal changes are limited to alterations in the vessels.

A consideration of the side in which the suspect kidney was found demonstrates two remarkable findings. The first, that the right kidney has been affected in approximately two-thirds of the series; and the second, that it appears to offer a significantly greater chance of cure. In 94 cases the lesion was on the right side and 50 were relieved of the hypertension. In 52 lesions of the left kidney only 20 obtained relief. These figures are all the more remarkable because, as far as I am aware, the only lesions which show a marked predilection for the right kidney are the pyelitis, hydronephrosis and hydro-ureter associated with pregnancy, and although there is a large number of cases of hydronephrosis in the series, nearly two-thirds of them were bad results.

Renal Function Tests

The urea clearance and water concentration and dilution tests are observations on total renal function. The former reveals with a degree of accuracy sufficient for clinical purposes the ability of the renal tract to excrete salts in the urine, and the latter the capacity of the tract for conserving the fluid medium of its environment. In this connexion Fullerton in 1923 showed that oliguria from one kidney may be masked by diuresis from the other, and in 1949 it was demonstrated (Maitland) that in hydronephrosis the appearances on intravenous pyelography were no indication of the quality of the urine secreted by the kidney. The earlier work demonstrates the need for divided renal function tests; the latter suggests that intravenous pyelography is inadequate by itself, when accurate knowledge of the function of each kidney is required. The additional tests which may be used are chromocystoscopy with indigocarmine or phenolphthalein as an indicator, or differential renal analysis. More than one of these may on occasion be required.

Examination of the figures made available from the questionnaires shows that a little more than half the cases were submitted to a urea clearance as a test of total renal function and a much smaller number to the water concentration and excretion tests. Intravenous pyelography was employed universally as the test of divided renal function and, with a small number of clinics as exceptions, it was apparently the sole test employed. In contrast, all the American cases and most of the others forming the comparative series, had a thorough investigation made of divided renal function. Since half the cases present as hypertension without renal symptoms, and this half has a better prognosis in the series from the literature but not in that under discussion, it appears that more detailed enquiries into divided renal function are valuable in relation to the results obtained. Bad results in many cases are due to bilateral renal disease and tests of total renal function and intravenous pyelography are not always sufficiently comprehensive to reveal this. A more complete investigation may not sig-

nificantly increase the total of good results from nephrectomy. It undoubtedly diminishes the bad ones by revealing the cases more likely to benefit from sympathectomy and those which should be left alone.

Treatment and Results

The methods of treatment available are expectant, nephrectomy, and sympathectomy either by itself or in addition to nephrectomy. Expectant treatment is on the usual lines of a salt-free diet with small protein content and rather restricted fluid intake, with a sedative at night as required. It should be employed in cases unsuitable for nephrectomy or sympathectomy, possibly as a post-operative routine and as a preliminary to more active measures in cases of doubt, for urgency presses treatment only in cases associated with gross retinal changes.

Nephrectomy is indicated in surgical renal disease affecting one kidney in which the opposite kidney is of normal function. It is also indicated in cases in which exhaustive investigations demonstrate clearly that the function of one kidney is grossly affected and the other has escaped sufficiently to undertake the function of both. When doubt exists of the functional capacity of the more normal kidney to do so, bilateral splanchnicectomy should be employed; and in cases where the nephrectomy has been only partially successful, contralateral sympathectomy appears to be of considerable value.

Table I

Treatment	Results Good	Bad
Nephrectomy	59	70
Nephrectomy and sympathectomy	4	4
Sympathectomy	2	1
Expectant	3	1

It was hoped that the survey would have produced a larger number of cases treated by splanchnicectomy either alone or in association with nephrectomy. The small number shown has no statistical significance but it does suggest that these methods are of some value, for it may be fairly assumed that the cases in which they were employed with benefit would have been unchanged by nephrectomy or were unsuitable for it. The results obtained from these methods are shown in Table I and it will be seen that nephrectomy alone gave good results in 45·7%, splanchnicectomy in association with nephrectomy produced 4 good results out of 8 cases, and splanchnicectomy by itself gave good results in 2 out of the 3 in which it was employed.

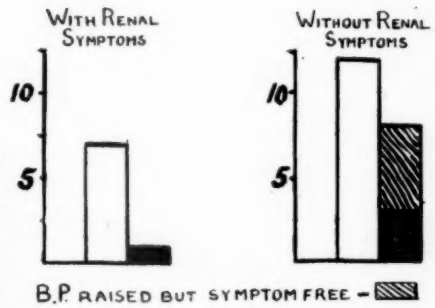

Fig. 1.—Results at five years. Potential survivors 41; actual survivors 28.

It was noted that 41 cases could have survived five years. They have been separated out and this has provided information of some value. From the 41 potential survivors over five years there were actual reports after five or more years in 28. Fig. 1 shows that 19 of these 28 of whom reports are available were good results, 5 were symptom-free but had continuing hypertension, and the remaining 4 were bad results. These figures suggest that results, by the standards used here, remain so but that in a certain proportion of cases continuing hypertension may not be a bar to survival. The continuing hypertension in these 5 cases was not a considerable elevation. These results also suggest that if a case is a bad result it is unlikely to survive five years.

Comparison of the results on a pathological basis has been made with all the cases collected from the literature. The figures obtained by this means are shown in Table II. This shows that in pyelonephritis the results in this series are better than those from elsewhere, which gave 43·4% of good results against 57% in the series under review. The reverse was true in hydronephrosis, the comparative figures being 43·7% for the literature and 38·8% for this series. Among the small groups listed it is of interest to note that the removal of a kidney subsequently reported as normal has, in the reported two cases, produced a complete cure lasting some years.

Condensation of the information gained from this series gives us the following clinical picture of unilateral renal hypertension. The condition forms less than 5% of all cases of hypertension; it is rather more common in females but appears to have a slightly better prognosis in males. In more than half the cases no renal symptoms are present and in this series the right kidney has been affected twice as often as the left, and has for some reason produced rather a higher proportion of good results. Nephrectomy either alone or with contralateral splanchnicectomy and bilateral splanchnicectomy have all given good results, and in the absence of gross retinal changes there is no contra-indication to expectant treatment until a decision is taken on which of the more active methods of treatment is most appropriate. If the diastolic pressure is below 100 mm.Hg after one year, a good prognosis over a long period is probable in the absence of further renal disease or complications, and the best results may

be expected in cases of pyelonephritis, although good results may be obtained in all forms of renal disease whether it is symptomless or not.

TABLE II.—RESULTS GROUPED UNDER PATHOLOGY

	Literature		Questionnaires		
	Total	Good%	Good	Bad	Good%
Atrophic pyelonephritis ..	205	43·4	32	24	57
Hydronephrosis	96	43·7	28	44	38·8
Pyonephrosis	31	33	—	1	—
Tubercle	22	40·9	2	3	—
Tumour	14	28	4	1	—
Calculus	8	12·5	1	3	—
NORMAL	1	100	1	—	—
Miscellaneous	15	60	1	1	—

Since the closest approximation to the "Goldblatt" kidney known in human pathology is unilateral pyelonephritis, this group of 56 cases has been analysed separately in the same manner as the whole series. This reveals that this condition follows a similar pattern.

UNILATERAL PYELONEPHRITIS

It is more common in females but in them has a better prognosis. Cases presenting without renal symptoms are also more common and have a better prognosis.

There is the same prevalence on the right side and when that side is affected there is a much better chance of cure.

13 out of the 56 cases could have survived five years and there are reports for them all. 10 are good results, 2 bad, and 1 child is surviving ten years later, aged 24 years, with blood pressure 180/110.

The repetition of the extraordinary incidence on the right side with an associated higher cure rate in this group as well suggests that this kidney must be affected more often by itself than the left. No explanation can be offered for this but it seems a point worth further study in relation to pyelitis unaccompanied by hypertensive disease.

In conclusion and in order to justify the firmness of my remarks on renal function tests and illustrate their value in separating the cases into groups suited to the different treatments I should like briefly to describe some cases from my records. None of them had renal symptoms.

Case I.—Female, aged 16 years.

Increased pressure (170/120) was discovered at a routine examination. Intravenous pyelography shows poor function of the left kidney, the right being normal (Fig. 2). The differential renal analysis demonstrates very poor function of the left kidney and not very good on the right (Table III). She has been observed for a year

TABLE III

Case	Standard clearances Right kidney	Left kidney
I	10·25	1·06*
II	11·09*	29·43
III:		
Pre-op ..	4·47*	4·93
Post-op. ..	25·94	6·64
IV:		
Pre-op. ..	0·81*	6·92
Post-op. ..	8·85	14·83
V:		
Pre-op. ..	14·61	3·59*
Post-op. ..	10·06	6·2
One year later	13·468	0·224

These clearances are calculated from figures which were displayed in full at the meeting but are not shown here in order to save space.

The kidney involved is marked with an *.

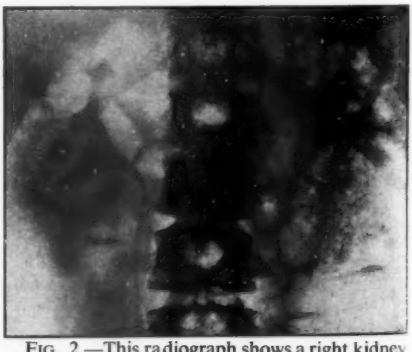

FIG. 2.—This radiograph shows a right kidney which is normal in outline and function. The left is just discernible functioning poorly over the twelfth rib.

without any change taking place in the renal function and, as she has a previous history of retention in infancy and early childhood due to some inflammatory disturbance of the urinary tract, is regarded as a doubtful case for active treatment. In any event, at her age there is no urgency about the decision. This case is regarded as suitable for expectant treatment because of doubtful function in the contralateral kidney.

Case II.—Female, aged 57.

Admitted to a medical ward complaining of abdominal pain and vomiting, and found to have a blood pressure of 265/130. The intravenous pyelograms are demonstrated in Fig. 3; both renal outlines are visible, but the right is not as well outlined as the left and a small calculus is seen in the upper minor calyx. The differential renal clearance revealed that the right kidney was functioning at less than half the capacity of the left (Table III), and the urine on that side contained *B. coli* and pus cells. In view of these findings, and with a good deal of misgiving, right nephrectomy was performed. The patient is still well almost five years after

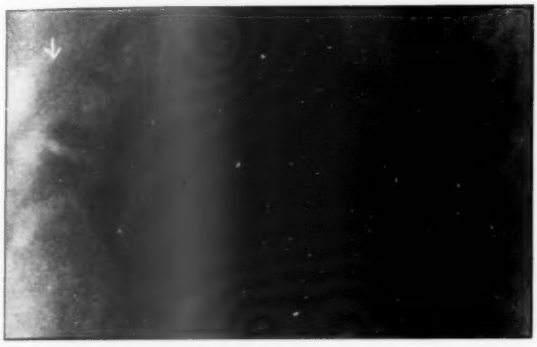

FIG. 3.—These pyelograms show a fairly normal outline on the left side. The right is not so well outlined, the arrow marks a tiny calculus in the uppermost calyx.

the nephrectomy, with a blood pressure of 170/96. Pathological examination of the kidney revealed a wedge of atrophic pyelonephritis which, from its appearance, suggested that it had had a vascular origin.

This case demonstrates that in the acute inflammatory or vascular lesion of a kidney associated with hypertension, a good result may be obtained even in an elderly patient.

Case III.—Female aged 18 years, whose intravenous pyelograms show the irregular outline of chronic pyelonephritis (Fig. 4), had her hypertension discovered at a routine medical examination. It was 200/140. Differential renal analysis showed a low renal function on both sides but rather lower on the right than the left (Table III), and the bladder urine contained pus cells and coliform organisms. A right splanchnicectomy

FIG. 4.—This radiograph illustrates the eighteen-minute film of an intravenous pyelography series. It shows the changes of chronic pyelonephritis affecting both kidneys.

was performed by Mr. W. Arthur Mackey nearly three years ago, the renal function of that kidney improving by sixfold. No further operative procedure has been done and three years later her blood pressure is still 170/100, she is without symptoms and working a full day in an office.

Cases IV and V were submitted to splanchnicectomy by Mr. Sloan Robertson and fall into a group in which the kidney affected shows as a thin spastic organ on intravenous pyelography.

Case IV.—Female, aged 41.

History of headache for three years without previous kidney trouble. During her solitary pregnancy there had been no renal disease but severe vomiting continued throughout. Her blood pressure was 250/140. The intravenous pyelogram is illustrated in Fig. 5. It shows normal function, the left renal outline being normal, but the right is spastic in appearance and apparently concentrating the dye. The differential renal analyses done before and after the first splanchnicectomy are shown in Table III. They reveal that on the first occasion there was very poor function indeed from the right kidney and the left also was not very good. After the operation on the right side there was a great increase of function on that side and also some increase of function

on the left. Three years after the operation her blood pressure is 160/100 and she is doing a full day of exacting mental work and may, I think, be regarded as a good result and likely to remain so. Her intravenous pyelograms taken approximately a year after the second splanchnicectomy are shown in Fig. 6. They are normal, and the silver clips seen outline the extent of the sympathectomy.

FIG. 5.—This is an intravenous pyelogram demonstrating normal function on both sides. The outline on the left is normal; on the right it is spastic and there is concentration of the dye.

FIG. 6.—This radiograph illustrates the appearances in the same patient as Fig. 5 one year later. Function and outline on both sides are normal. (The silver clips outline the sympathectomy.)

Case V.—Male, aged 42.

Influenza five months previously which was followed by severe frontal headache. Past history of nephritis thirteen years before. His blood pressure was 220/140 and an exudative retinitis with flame-shaped hæmorrhages was present in both optic fundi. The intravenous pyelograms demonstrate normal function and outline in the right kidney. The function of the left was somewhat delayed and its pelvis was small and spastic (Fig. 7). The differential renal function test before operation showed quite a good function on the right side but poor on the left. Table IV also demonstrates these function tests done three weeks after the splanchnicectomy on the left side and a year after the operation. They demonstrate that there was little improvement following the operation and a year later the function on the left side was actually worse, although at that time the blood pressure was extremely high and the pyelographic changes were more marked (Fig. 8). This patient represents

FIG. 7.—These pyelograms show normal function and somewhat large outline in the right kidney. The left is small and spastic, and there was delay in excretion.

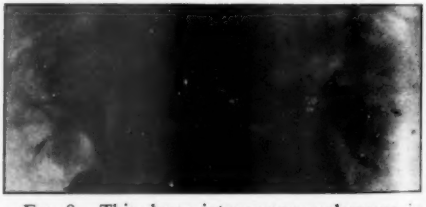

FIG. 8.—This shows intravenous pyelograms in the same patient as Fig. 7 one year later. The most noticeable feature is the increase in spasticity of the left kidney, which coincided with a hypertensive crisis.

a problem in treatment. It is likely he would have been a bad result under any method. He certainly has been so with splanchnicectomy. Whether any improvement in the result could have been obtained by removing the left kidney and doing a contralateral splanchnicectomy cannot be known. It was considered but was ruled out owing to the previous history of nephritis and the poor renal function as demonstrated by differential renal analysis. He is still alive nearly four years later, but has severe cerebrovascular damage and is confined to bed.

The following interesting points arise from these cases: Firstly, some patients will do better if treated expectantly either permanently or during a period of observation, and secondly, differential renal function tests of some accurate type are necessary in choosing the form of treatment which will be of lasting benefit. In some cases they provide essential evidence for deciding which should be left

alone, which should have nephrectomy and which would benefit more from splanchnicectomy. The importance of making this decision correctly has been underlined by the evidence displayed in this Discussion of the excellent prognosis at five years, provided an accurate choice has been made.

ACKNOWLEDGMENTS

It is a great pleasure to thank the many colleagues who returned questionnaires; this help was invaluable. I have also to thank Sir John W. McNee for Case II, and the Editor of the *Lancet* for permission to republish Cases III, IV and V. The radiographs are reproduced by courtesy of Dr. S. D. Scott Park, Director of the Radiology Department, Western Infirmary, Glasgow.

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The President said that Dr. Wright had classified the varieties of hypertension and indicated the types which should have urological investigation. He had left no doubt that the percentage of total sufferers likely to be helped by nephrectomy was very small.

Mr. Maitland had reviewed the results of surgical treatment in 146 cases from information obtained by his questionnaire and compared the data with that obtained from United States and Continental literature. The figures showed that only in about 5% of the total was there acceptable evidence that unilateral renal disease caused the hypertension, and that only a small proportion of that percentage could be regarded as suitable for surgical treatment.

Mr. J. G. Yates-Bell gave figures dating from 1942. He had used the same criteria as Mr. Maitland regarding the diastolic and the systolic blood pressure. During the intervening ten years out of his 300 nephrectomies Mr. Yates-Bell had been able to trace 39 associated with hypertension. In those 39 cases there had been 14 failures, 12 successful cases over five years, 12 under five years, and 1 under two years. Those figures were rather higher than the 20% average successes reported recently by Wayman and Ferriss (1952), and they agreed with Mr. Maitland's findings.

Mr. Yates-Bell had adopted the same two classifications as had Dr. Wright and Mr. Maitland: viz. Group 1, in which hypertension was the symptom calling for treatment; Group 2, treatment was for the urinary disease associated with gross hypertension. In addition he had Group 3, urinary disease associated with slight definite hypertension in young people.

In Group 1 there were 3 failures and 7 successes. None of these were stone cases.

In Group 2 there were 14 cases of which 6 had proved successful. 5 were cases of hydronephrosis and 1 case of papilloma of the renal pelvis. There were 8 failures, 7 of which were stone cases, the other being an aneurysm of the renal artery.

In Group 3 there were 15 cases dealt with, 12 of which were successful, and of these 5 were hydronephrosis; 3 chronic pyelonephritis and 4 tuberculosis.

Of 14 failures in all 3 groups, 10 were stone cases, and all the cases had failed within three years.

An interesting case was that of a male, aged 40, who had hæmaturia in 1943 from an apparently simple papilloma near the left ureter. The intravenous pyelography was normal, blood pressure of 140/105 was, admittedly, a little high. Two months later, in spite of cauterization, the base of the papilloma was thought to be malignant. Simultaneously the patient complained of persistent headache and blood pressure was 180/135. The intravenous pyelography showed no excretion from the left kidney. The patient was treated in July 1943 by partial cystectomy and insertion of radon seeds and re-implantation of the obstructed left ureter. The blood pressure returned to 140/100. There was no recurrence of the growth, but headaches returned eight years later, in 1951, when blood pressure was back to 180/140 and the intravenous pyelography still appeared to be normal. Indigocarmine excretion was delayed from the left kidney. An empirical left nephrectomy was carried out, since when blood pressure had fallen and remained at 140/100.

It seemed worth emphasizing that 4 patients with renal tuberculosis and hypertension had been relieved by nephrectomy.

Prognosis in all cases had been very difficult. In the cases mentioned, chronic pyelonephritis and hydronephritis had given the best results; stone cases gave by far the worst results.

REFERENCE.—WAYMAN, T. B., and FERRISS, E. R. (1952) *J. Urol.*, **67**, 37.

Mr. M. F. Nicholls agreed emphatically with Mr. Maitland that it was necessary to investigate the function of each kidney separately; personally he had himself several times refused to operate because the functions of the kidneys had been found to be almost identical.

The following case illustrated the points previous speakers had emphasized.

Woman, aged 21, admitted to St. George's Hospital in 1948 under Dr. Alastair Hunter complaining of

swelling of the ankles and headache over two or three years. There was no other history and no history connected with micturition. Blood pressure was 210/130 and the patient's fundi showed early papillœdema; blood urea was 26 mg.%. The left kidney had no function; the right was normal. The left kidney was removed, it was tiny with thickened vessels and comparatively dilated calices. Histologically this was the result of pyelonephritis dating from infancy. The effect of nephrectomy was disappointing. The blood pressure was reduced immediately after operation from 210/130 to 140/100 and the fundal changes were said to be improved. But she had been readmitted to hospital in May 1949 with headache and a blood pressure of about 180/120.

The patient had last been seen in August 1951 when she was said to be well and happy but with occasional headaches. She had married during the interval.

This case, although apparently of the most favourable type, must be classified as a failure.

Mr. Theo L. Schofield (for Professor Charles Wells, Liverpool) based his remarks on a review of 116 cases of hypertension treated surgically. Of these, 4 patients had had nephrectomy alone and 4 nephrectomy with bilateral thoracolumbar sympathectomy.

Of the first group, two were unsuccessful and subsequent post-mortem showed advanced hypertensive disease of the remaining kidney. In 2 the results were excellent. Both were young girls, aged 13 and 17; each had a non-functioning right kidney, found to be small and atrophic on retrograde pyelography. Both specimens showed atrophic pyelonephritis. After four years and one year respectively the blood pressure remains within normal limits.

In the group treated by nephrectomy and sympathectomy, all have been successful, but on review it was thought that probably the sympathectomy had been unnecessary. In essential hypertension the blood pressure falls immediately to its lowest level after completion of the sympathectomy and then it slowly rises over a period of about twelve months, by which time the majority have regained their pre-operative level. In the 4 cases of hypertension with unilateral renal disease there was a fall in blood pressure after nephrectomy and another fall on completion of sympathectomy, but it was not until three to eight months after operation that the blood pressure came to its lowest level.

There was a marked fall immediately in the cases with nephrectomy alone, but the final low level of blood pressure was likewise not reached until six months following operation.

Of the 6 successful cases, 4 were associated with atrophic pyelonephritic kidneys (hypoplastic kidney), 1 with renal calculus and atrophic pyelonephritis and 1 with hydronephrosis. Unilateral atrophic pyelonephritis is not always associated with hypertension—2 such kidneys have been removed in the last month, both patients were normotensive.

Mr. J. P. Mitchell (for Mr. A. Wilfrid Adams) presented 2 cases:

Case I.—Woman, aged 70, referred by Dr. Orr-Ewing in May 1949 with a history of attacks of severe pain in the right loin, associated with marked frequency. On examination there was a large mass in the right side of the abdomen. The blood pressure was 260/160, and the blood urea was normal.

X-ray showed a row of opacities stretching from the right to the left iliac fossa. On retrograde pyelogram these proved to be extensive renal calculi.

Operation was advised despite and not in the least in the hope of curing the hypertension. A large calculus hydronephrosis was found and immediately after nephrectomy the systolic pressure fell to 110.

The patient was relieved of her pain and frequency, and for a year the blood pressure remained at 150/70. But in March 1952, three years after operation, it had relapsed slightly to 175/100.

Case II (previously reported to the Section by Mr. Adams in January 1947).—Woman, aged 78, first seen in 1945 with four months' history of progressive constipation alternating with occasional diarrhœa. The patient was breathless and could walk only a very short distance. The blood pressure was 250/150. A mass was palpable in the right side, but on exploring the abdomen it was found to be a Riedel's lobe. However, behind this was a very small aplastic kidney, to which no less than five arteries were running. After nephrectomy the blood pressure fell to 160/100, where it remained for sixteen months. In May 1948 she died one week after a stroke.

On examining the kidney with the naked eye one was impressed by the prodigious supply of arteries. The kidney showed a veritable leash of five quite sizable vessels.

The feature of particular interest in the 2 cases was the age of the patients. Both were septuagenarians and both showed a sustained fall in blood pressure following nephrectomy. The blood pressure remained normal for more than one year after operation. Both cases afforded a striking example of the occasional responsibility of unilateral renal disease for raised blood pressure, and even in the 8th decade of life the changes of hypertension are not irreversible.

Professor V. W. Dix said that his own cases were included in Mr. Maitland's large series. There were some points of importance in assessing this method of treating hypertension. A large series of cases was published in the *Journal of the American Medical Association* about 1940 on the fall of blood pressure which occurred after non-specific operations on patients with hypertension. These observations could not be disregarded until further observations had been made. Mr. Maitland had mentioned that there should always be a differential estimation of renal function before operation was undertaken. The only differential renal function test used by the speaker had been an intravenous injection of indigocarmine, but it was clearly better to have a more exact estimate.

All patients who were going to have a nephrectomy in the hope that it would cure hypertension

should, in future, rest in bed for a week before operation and daily blood pressure readings should be made. The fall of blood pressure after operation was, he thought, of some prognostic significance. In those patients who are likely to be cured the blood pressure has returned to a normal figure on the day after operation and remains normal. In other patients it rises again on the third or fourth day and usually becomes fixed at a level about half-way between the pre-operative figure and the normal figure. He believed that a normal figure every day for the first fortnight after the operation indicated a good prognosis.

Mr. David Band said that bilateral splanchnicectomy had given most satisfactory results in the treatment of selected cases of essential hypertension. The blood pressure had fallen and, more important, the patient had obtained symptomatic relief.

In the investigation of hypertension whether essential or renal, physician and urologist should arrange for full collaboration with an interchange of views when their respective examinations have been completed. Should hypertension be present in association with unilateral renal disease, the rational operative treatment would appear to be a combination of splanchnicectomy and nephrectomy on the affected side. A Bernard Fey incision gave an excellent approach. Relief of hypertension by this dual operative treatment suggested that the diseased kidney had caused the hypertension, and no further operative intervention was necessary. But should the blood pressure again rise after nephrectomy and unilateral splanchnicectomy, a second-stage operation would be required and a contralateral splanchnicectomy carried out. To attempt splanchnicectomy following nephrectomy was a difficult operation, and the combination of unilateral splanchnicectomy and nephrectomy was a reasonable procedure.

Mr. E. W. Riches said that he personally had rarely seen cases of hypertension cured by nephrectomy. Mr. Maitland had shown some patients who were undoubtedly improved by surgical treatment, but Dr. Wright had stated that he had had only two successful cases out of the enormous number of 10,000 patients! There had also been conflicting reports on the effects of splanchnicectomy.

He (Mr. Riches) was not particularly happy about differential renal function tests carried out by means of a ureteric catheter. The fallacies associated with collecting urine by that means were well known and some of Mr. Maitland's specimens were as small as 0·5 ml. Such a specimen would be rejected by some pathologists. Any differential renal function test must be accurate and probably the indigocarmine test was as good as any at present despite differences in its interpretation.

Moderate hydronephrosis in the presence of hypertension presented another problem. Was one to do a nephrectomy, or the plastic operation one would have done without the hypertension? So far he had been doing the nephrectomy rather than the plastic operation, but he did not think there were any cases in which there had been a permanent lowering of blood pressure.

The distinction between congenital and acquired renal aplasia was also sometimes difficult even to the pathologist.

Mr. Yates-Bell had mentioned tubercle; at the March 1952 meeting of the Section he (Mr. Riches) had mentioned 2 cases of functionless caseous renal tuberculosis. Both had hypertension, and nephrectomy had caused lowering of the blood pressure but it was too early yet to say whether that would be permanent.

Mr. D. Innes Williams pointed out that ureteric catheter specimens measured the function of the kidney as a whole. It was not impossible for a small section of the kidney to be ischæmic and to be producing the hypertensive factor without making a significant difference to the total function as measured by the concentration of the urine. A case from Gt. Ormond Street recently published illustrated this point: the removal of a congenitally small but normally functioning kidney had brought down the blood pressure from a very high figure, and the readings had now been practically normal for over a year.

In some cases it seemed unlikely that fibrosis alone was responsible for the ischæmia which caused the hypertension. The recent observation of a transient attack of high blood pressure following a hemi-nephrectomy suggested that external compression—in this case by a tightly stitched capsule—might be a factor.

Mr. Alex. E. Roche said that, in relation to any medical suggestion of nephrectomy for hypertension associated with unilateral renal disease, the rule he made for himself was not to do a nephrectomy unless it would have been indicated anyway, in the absence of hypertension.

Mr. A. W. Badenoch said that in the large number of cases which had been referred to by the openers he had not noticed that any had been reported in which there had been an injury to a kidney. Ischæmia and fibrosis were likely to follow injury to the kidney and he had been greatly interested in whether gross ruptures of the kidney were followed by hypertension. It had been suggested that a rise in blood pressure should follow injury; in 1945 Abernethy published a few cases in which there had been a temporary rise in the few weeks following injury. In the speaker's own series of some 50 cases, he had not observed the occurrence of hypertension.

It had not been possible to follow a high proportion of these cases. A considerable number had

been Service personnel. There were, however, 3 cases in particular to which he would like to refer. In 2, a complete pole had either been avulsed or destroyed, while the remaining part of the kidney functioned well. Neither case had been operated on. They had been followed up for a period of twelve months and in neither case did hypertension develop.

He had had the opportunity of seeing a case where the kidney had been pulled off at the hilum. The patient was severely injured, as twelve ribs were fractured on one side, but the clinical effect of the kidney injury was slight and it was not noticed at the time of the accident, or during the immediate convalescent period. Four months after the accident, attention was drawn to the renal tract and the kidney was not functioning on that side. It was explored and found to be replaced by a fibrous mass. Each of these cases had something of the "Goldblatt" kidney about them, but there was no clinical evidence of hypertension after four to twelve months from the time of injury.

He asked Dr. Wright and Mr. Maitland if there had been a history of renal injury in any case of established hypertension.

Mr. Hugh Donovan said there were two good ways in which one could make certain about the function of the kidney left behind or to be left behind. One was through biopsy; the other, a less troublesome method, was to test the function of the remaining kidney after its fellow had been removed. Such a study, when correlated with the late behaviour of the blood pressure, should be profitable.

Mr. A. I. L. Maitland said in reply to Mr. Band: All patients had a week's rest in bed and a sodium amytal test prior to nephrectomy for hypertension with or without renal symptoms.

In reply to Mr. Riches' remarks relating to differential renal analysis it was true that the ureometer test could be fallacious, but what clinical test of renal function was not? In all cases in which serious decision rested on the results of such tests the wastage to the bladder at the end of the examination was measured separately and estimated. These figures had been omitted for the sake of clarity, but the precise technique had been described in various publications on the subject and included the use of a tuberculin syringe for delivering the urine to the ureometer. This permitted the analysis of smaller specimens with greater accuracy. It was right to be sceptical towards such tests. Mr. Maitland's own view was clearly demonstrated in Case I, where the renal standard clearances were 10·25 and 1·06 respectively, yet he had regarded the case as unsuitable for nephrectomy.

Referring to the manner of the fall in blood pressure which occurs, Verney and Vogt described as one of the features of hypertension due to renal disease the return of the blood pressure to normal within half an hour of nephrectomy in successful cases. This had been Mr. Maitland's own experience.

Without prior notice, no definite information could be given of the way in which the blood pressure fell in splanchnicectomy. It was probable that the fall was slow. Was the histological picture of pyelonephritis one that was peculiar to infection? If so, was it infection of the renal tissue with organisms or could it be toxic changes produced in the renal architecture by distant infection, or was the condition present from childhood as a congenital hypoplasia of the kidney? The histology of all these conditions could be very similar in appearance. The last condition could be met with right up to 70 years of age, as Mr. Mitchell had shown in his 2 cases which were included in the series. This problem should be put to the pathologists and their assistance requested in its solution. Professor G. L. Montgomery, of Glasgow University, had said that any inflammatory disease producing symptoms or not would bring about changes in the kidney which could be seen many years later in the kidney. That should be borne in mind in relation to pyelonephritis.

In reply to Mr. Badenoch: An extensive survey of the literature had revealed 4 cases of renal trauma, all of which had been insufficiently documented; they had been followed up only for a few months, and the elevation of blood pressure had not amounted to hypertension. There were no cases of injury in the series which he had reviewed.

Dr. J. H. Wright stressed that the effect of emotion must be borne in mind when assessing the effect of treatment on hypertension. The relief of pain or of intra-abdominal pressure could lead to a fall in blood pressure.

Labile blood pressure had not been dealt with in detail, but the tables presented showed that cases fell into two groups: those with fixed hypertension, i.e. a hypertension which persisted during the course of the investigation; and those with labile blood pressure.

Mr. Maitland had included in his series one case which he had termed "normal".

That so-called normal patient was a girl, aged 21, whose blood pressure was systolic 230 mm.Hg, diastolic pressure 160. She had gross papillœdema and albuminuria 6 parts. Dr. R. A. Kemp Harper carried out intravenous pyelography which showed a non-functioning right kidney. An ascending pyelogram showed clubbing of the calyces of the right kidney. The kidney was removed by Mr. A. H. Jacobs. Immediately following operation the blood pressure fell to 120/80. Albuminuria disappeared after a few weeks. She had remained well since then. Her blood pressure still remained in the region of 120/80. Recently she had given birth to a full-term child after an uneventful pregnancy.

It was wrong to classify this case as "normal"; surely there must have been some abnormality not manifest to the pathologist.